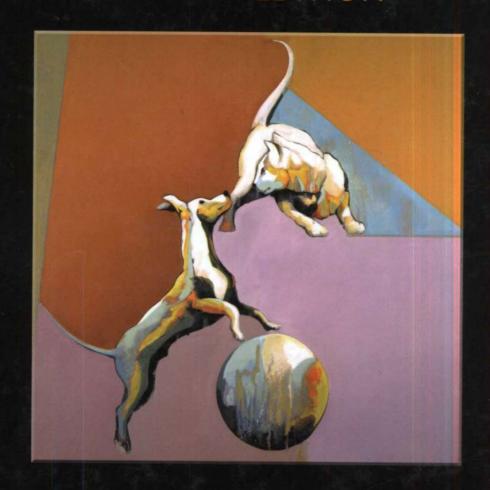
# SMALL ANIMAL INTERNAL MEDICINE

FOURTH EDITION



Richard W. Nelson C. Guillermo Couto

Grauer • Hawkins • Johnson • Lappin Scott-Moncrieff • Taylor • Ware • Watson • Willard

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SMALL ANIMAL INTERNAL MEDICINE

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We would like to dedicate this book to Kay and Graciela.

This project would not have been possible without their continued understanding, encouragement, and patience.

# Preface

In the fourth edition of *Small Animal Internal Medicine*, we have retained our original goal of creating a practical text with a strong clinical slant that is useful for both practitioners and students. We have continued to limit authorship, with each author selected for clinical expertise in his or her respective field, to ensure as much consistency as possible within and among sections of the book. We have continued to focus on the clinically relevant aspects of the most common problems in internal medicine, presenting information in a concise, understandable, and logical format. Extensive use of tables, algorithms, cross-referencing within and among sections, and a comprehensive index help make *Small Animal Internal Medicine* a quick, easy-to-use reference textbook.

### **ORGANIZATION**

The book contains 14 sections organized by organ systems (e.g., cardiology, respiratory) or when multiple systems are involved, by discipline (e.g., oncology, infectious diseases, immune-mediated disorders). Each section, when possible, begins with a chapter on clinical signs and differential diagnoses and is followed by chapters on indications, techniques, and interpretation of diagnostic tests; general therapeutic principles; specific diseases; and finally a table listing recommended drug dosages for drugs commonly used to treat disorders within the appropriate organ system or discipline. Each section is supported extensively by tables, photographs, and schematic illustrations, including many algorithms, which address clinical presentations, differential diagnoses, diagnostic approaches, and treatment recommendations. Selected references and recommended readings are provided under the heading "Suggested Readings" at the end of each chapter. In addition, specific studies are cited in the text by author name and year of publication and are included in the Suggested Readings.

### **KEY FEATURES OF THE FOURTH EDITION**

We have retained all of the features that were popular in the first three editions, and have significantly updated and expanded the new fourth edition. New features include:

- Thoroughly revised and updated content, with expanded coverage of hundreds of topics throughout the text
- The expertise of three new authors for the sections dealing with hepatobiliary and exocrine pancreatic disorders, metabolic and electrolyte disorders, and immunemediated disorders
- New, separate sections and expanded focus on hematology and immunology

- The section focusing on immune-mediated disorders has been reorganized to include chapters on:
  - Current recommendations and interpretation of diagnostic tests
  - An overview of commonly used drugs for treating immune-mediated disorders
  - Treatment protocols for managing common immunemediated disorders
- Hundreds of new clinical photographs, the majority in full color
- Algorithms throughout the text to aid readers in the decision-making process
- Extensive cross-referencing to other chapters and discussions, providing a helpful "road map" and reducing redundancy within the book
- Hundreds of functionally color-coded summary tables and boxes to draw the reader's eye to quickly accessible information, such as:



Etiology



Differential diagnoses



Drugs (appearing within chapters)



Drug formularies (appearing at the end of each section)



Treatment



General information (e.g., formulas, clinical pathology values, manufacturer information, breed predispositions)

Finally, we are grateful to the many practitioners, faculty, and students worldwide who provided constructive comments on the first three editions, thereby making it possible to design an even stronger fourth edition. We believe the expanded content, features, and visual presentation will be positively received and will continue to make this book a valuable, user-friendly resource for all readers.

RICHARD W. NELSON C. GUILLERMO COUTO

# Acknowledgements

We would like to extend our sincerest thanks to Greg, Eleanor, Cheri, Michael, Sue, Wendy, and Mike for their continued dedication and hard work to this project; to Catharine, Penny, and Sean for their willingness to become involved in this project; and to Tony Winkel, Maureen Slaten, Celeste Clingan, and many others at Mosby for their commitment and latitude in developing this text.

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# PART ONE

### CARDIOVASCULAR SYSTEM DISORDERS

Wendy A. Ware

## CHAPTER

# Clinical Manifestations of Cardiac Disease



### CHAPTER OUTLINE

SIGNS OF HEART DISEASE SIGNS OF HEART FAILURE

Weakness and Exercise Intolerance Syncope

Cough and Other Respiratory Signs

THE CARDIOVASCULAR EXAMINATION

Observation of Respiratory Pattern

Mucous Membranes

Jugular Veins

Arterial Pulses

Precordium

Evaluation for Fluid Accumulation

Auscultation

### SIGNS OF HEART DISEASE

Signs of heart disease can be apparent even if the animal is not clinically in "heart failure." Objective signs of heart disease include cardiac murmurs, rhythm disturbances, jugular pulsations, and cardiac enlargement. Other clinical signs that can result from heart disease include syncope, excessively weak or strong arterial pulses, cough or respiratory difficulty, exercise intolerance, abdominal distention, and cyanosis. However, noncardiac diseases can cause these signs as well. Further evaluation using thoracic radiography, electrocardiography (ECG), echocardiography, and sometimes other tests is usually indicated when signs suggestive of cardiovascular disease are present.

### SIGNS OF HEART FAILURE

Cardiac failure occurs when the heart cannot adequately meet the body's circulatory needs or can do so only with high

filling (venous) pressures. Most clinical signs of heart failure (Box 1-1) relate to high venous pressure behind the heart (congestive signs) or inadequate blood flow out of the heart (low output signs). Congestive signs associated with rightsided heart failure stem from systemic venous hypertension and the resulting increases in systemic capillary pressure. Congestion behind the left side of the heart produces pulmonary venous hypertension and edema. Biventricular failure develops in some animals. Chronic left-sided congestive heart failure can facilitate the development of rightsided signs when pulmonary arterial pressure rises secondary to pulmonary venous hypertension. Signs of low cardiac output are similar regardless of which ventricle is primarily affected, because output from the left heart is coupled to that from the right heart. Heart failure is discussed further in Chapter 3 and within the context of specific diseases.

# WEAKNESS AND EXERCISE INTOLERANCE

Cardiac output often becomes inadequate for the level of activity in animals with heart disease or failure. Impaired skeletal muscle perfusion during exercise, related to vascular and metabolic changes that occur over time, can reduce exercise tolerance. Increased pulmonary vascular pressures and edema also lead to poor exercise tolerance. Episodes of exertional weakness or collapse can relate to these changes or to an acute decrease in cardiac output caused by arrhythmias (Box 1-2).

### **SYNCOPE**

Transient unconsciousness associated with loss of postural tone (collapse) from insufficient oxygen or glucose delivery to the brain characterizes the clinical sign of syncope. Various cardiac and noncardiac abnormalities can cause syncope, as well as intermittent weakness (see Box 1-2). Syncope can be confused with seizure episodes (Fig. 1-1). A careful description of the animal's behavior or activity before the collapse event, during the event itself, and following the collapse, as



BOX 1-1

### Clinical Signs of Heart Failure

### Congestive Signs—Left († Left Heart Filling Pressure)

Pulmonary venous congestion

Pulmonary edema (causes cough, tachypnea, ↑ respiratory effort, orthopnea, pulmonary crackles, tiring, hemoptysis, cyanosis)

Secondary right-sided heart failure Cardiac arrhythmias

### Congestive Signs-Right († Right Heart Filling Pressure)

Systemic venous congestion (causes ↑ central venous pressure, jugular vein distention)

Hepatic ± splenic congestion

Pleural effusion (causes ↑ respiratory effort, orthopnea, cyanosis)

Ascites

Small pericardial effusion Subcutaneous edema Cardiac arrhythmias

### Low Output Signs

Tiring

Exertional weakness

Syncope

Prerenal azotemia

Cyanosis (from poor peripheral circulation)

Cardiac arrhythmias



### FIG 1-1

Syncope in a cat with intermittent complete AV block and delayed onset of ventricular escape rhythm. During these episodes the cat initially appeared dazed, then fell to her side and stiffened briefly. Within a few seconds she would regain consciousness and resume normal activity.

well as a drug history, helps the clinician differentiate among syncopal attacks, episodic weakness, and true seizures. Syncope is often associated with exertion or excitement. The actual event may be characterized by rear limb weakness or sudden collapse, lateral recumbency, stiffening of the forelimbs and opisthotonos, and micturition (Fig. 1-2). Vocalization is common; however, tonic/clonic motion, facial fits,



BOX 1-2

### Causes of Syncope or Intermittent Weakness

### Cardiovascular Causes

Bradyarrhythmias (second- or third-degree AV block, sinus arrest, sick sinus syndrome, atrial standstill)

Tachyarrhythmias (paroxysmal atrial or ventricular tachycardia, reentrant supraventricular tachycardia, atrial fibrillation)

Congenital ventricular outflow obstruction (pulmonic stenosis, subaortic stenosis)

Acquired ventricular outflow obstruction (heartworm disease and other causes of pulmonary hypertension, hypertrophic obstructive cardiomyopathy, intracardiac tumor, thrombus)

Cyanotic heart disease (tetralogy of Fallot, pulmonary hypertension and "reversed" shunt)

Impaired forward cardiac output (severe valvular insufficiency, dilated cardiomyopathy, myocardial infarction or inflammation)

Impaired cardiac filling (e.g., cardiac tamponade, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, intracardiac tumor, thrombus)

Cardiovascular drugs (diuretics, vasodilators)

Neurocardiogenic reflexes (vasovagal, cough-syncope, other situational syncope)

### **Pulmonary Causes**

Diseases causing hypoxemia Pulmonary hypertension Pulmonary thromboembolism

### Metabolic and Hematologic Causes

Hypoglycemia
Hypoadrenocorticism
Electrolyte imbalance (especially potassium, calcium)
Anemia
Sudden hemorrhage

### **Neurologic Causes**

Cerebrovascular accident Brain tumor (Seizures)

### **Neuromuscular Disease**

(Narcolepsy, cataplexy)

AV. Atrioventricular.

and defecation are not. An aura (which often occurs before seizure activity), postictal dementia, and neurologic deficits are generally not seen in dogs and cats with cardiovascular syncope. Sometimes profound hypotension or asystole causes hypoxic "convulsive syncope," with seizurelike activity or twitching; these convulsive syncopal episodes are preceded by loss of muscle tone. Presyncope, wherein reduced brain perfusion (or substrate delivery) is not severe enough to cause unconsciousness, may appear as transient "wobbliness" or weakness, especially in the rear limbs.



FIG 1-2
Syncope in a Doberman Pinscher with paroxysmal ventricular tachycardia. Note the extended head and neck with stiffened forelimbs. Involuntary micturition also occurred, followed shortly by return of consciousness and normal activity.

Testing to determine the cause of intermittent weakness or syncope usually includes ECG recordings (during rest, exercise, and/or after exercise or a vagal maneuver), complete blood count (CBC), serum biochemical analysis (including electrolytes and glucose), neurologic examination, thoracic radiographs, heartworm testing, and echocardiography. Other studies for neuromuscular or neurologic disease may also be valuable. Intermittent cardiac arrhythmias not apparent on resting ECG may be uncovered by 24-hour ambulatory ECG (Holter monitor), event monitoring, or in-hospital continuous ECG monitoring.

### Cardiovascular Causes of Syncope

Various arrhythmias, ventricular outflow obstructions, cyanotic congenital heart defects, and acquired diseases leading to poor cardiac output are the usual cardiac causes of syncope. Activation of vasodepressor reflexes and excessive dosages of cardiovascular drugs can also induce syncope. Arrhythmias that provoke syncope are usually associated with very fast or very slow heart rate and can occur with or without identifiable underlying organic heart disease. Ventricular outflow obstructions provoke syncope or sudden weakness if cardiac output becomes inadequate during exercise or if high systolic pressures activate ventricular mechanoreceptors, causing inappropriate reflex bradycardia and hypotension. Both dilated cardiomyopathy and severe mitral insufficiency can cause inadequate forward cardiac output, especially during exertion. Vasodilators and diuretics may induce syncope if given in excess. Syncope caused by abnormal peripheral vascular and/or neurologic reflex responses is not well defined in animals but is thought to occur in some patients. Syncope during sudden bradycardia after a burst of sinus tachycardia has been documented, especially in small breed dogs with advanced atrioventricular (AV) valve disease; excitement often precipitates such an episode. Doberman Pinschers and Boxers may experience a similar syndrome. Postural hypotension and hypersensitivity of carotid sinus receptors may infrequently provoke syncope by inappropriate peripheral vasodilation and bradycardia.

Fainting associated with a coughing fit (cough syncope or "cough-drop") occurs in some dogs with marked left atrial enlargement and bronchial compression, as well as in dogs with primary respiratory disease. Several mechanisms have been proposed, including an acute decrease in cardiac filling and output during the cough, peripheral vasodilation after the cough, and increased cerebrospinal fluid pressure with intracranial venous compression. Severe pulmonary diseases, anemia, certain metabolic abnormalities, and primary neurologic diseases can also cause collapse resembling cardiovascular syncope.

# COUGH AND OTHER RESPIRATORY SIGNS

Congestive heart failure (CHF) in dogs results in cough, tachypnea, and dyspnea. These signs also can be associated with the pulmonary vascular disease and pneumonitis of heartworm disease in both dogs and cats. Noncardiac conditions, including diseases of the upper and lower airways, pulmonary parenchyma (including noncardiogenic pulmonary edema), pulmonary vasculature, and pleural space, as well as certain nonrespiratory conditions, also should be considered in patients with cough, tachypnea, or dyspnea (see Chapter 19).

The cough caused by cardiogenic pulmonary edema in dogs is often soft and moist, but it sometimes sounds like gagging. In contrast, cough is an unusual sign of pulmonary edema in cats. Tachypnea progressing to dyspnea occurs in both species. Pleural and pericardial effusions occasionally are associated with coughing as well. Mainstem bronchus compression caused by severe left atrial enlargement can stimulate a cough (often described as dry or hacking) in dogs with chronic mitral insufficiency, even in the absence of pulmonary edema or congestion. A heartbase tumor, enlarged hilar lymph nodes, or other masses that impinge on an airway can also mechanically stimulate coughing.

When respiratory signs are caused by heart disease, other evidence, such as generalized cardiomegaly, left atrial enlargement, pulmonary venous congestion, lung infiltrates that resolve with diuretic therapy, and/or a positive heartworm test, is usually present. The findings on physical examination, thoracic radiographs, an echocardiogram if possible, and sometimes electrocardiography help the clinician differentiate cardiac from noncardiac causes of respiratory signs.

### THE CARDIOVASCULAR EXAMINATION

The medical history (Box 1-3) is an important part of the cardiovascular evaluation that helps guide the choice of diagnostic tests by suggesting various cardiac or noncardiac diseases. The signalment is useful because some congenital and acquired abnormalities are more prevalent in certain breeds or life stages or because specific findings are common



BOX 1-3

### Important Historic Information

Signalment (age, breed, gender)?

Vaccination status?

What is the diet? Have there been any recent changes in food or water consumption?

Where was the animal obtained?

Is the pet housed indoors or out?

How much time is spent outdoors? Supervised?

What activity level is normal? Does the animal tire easily now?

Has there been any coughing? When? Describe episodes.

Has there been any excessive or unexpected panting or heavy breathing?

Has there been any vomiting or gagging? Diarrhea?
Have there been any recent changes in urinary habits?
Have there been any episodes of fainting or weakness?
Do the tongue/mucous membranes always look pink, especially during exercise?

Have there been any recent changes in attitude or activity level?

Are medications being given for this problem? What? How much? How often? Do they help?

Have medications been used in the past for this problem? What? How much? Were they effective?

in individuals of a given breed (e.g., soft cardiac ejection murmur in normal Greyhounds).

Physical evaluation of the dog or cat with suspected heart disease includes observation (e.g., attitude, posture, body condition, level of anxiety, respiratory pattern) and a general physical examination. The cardiovascular examination itself consists of evaluating the peripheral circulation (mucous membranes), systemic veins (especially the jugular veins), systemic arterial pulses (usually the femoral arteries), and the precordium (left and right chest walls over the heart); palpating or percussing for abnormal fluid accumulation (e.g., ascites, subcutaneous edema, pleural effusion); and auscultating the heart and lungs. Proficiency in the cardiovascular examination requires practice but is important for accurate patient assessment and monitoring.

# OBSERVATION OF RESPIRATORY PATTERN

Respiratory difficulty (dyspnea) usually causes the animal to appear anxious. Increased respiratory effort, flared nostrils, and often a rapid rate of breathing are evident (Fig. 1-3). Increased depth of respiration (hyperpnea) frequently results from hypoxemia, hypercarbia, or acidosis. Pulmonary edema (as well as other pulmonary infiltrates) increases lung stiffness; rapid and shallow breathing (tachypnea) results as an attempt to minimize the work of breathing. An increased resting respiratory rate is an early indicator of pulmonary edema in the absence of primary lung disease. Large-volume



FIG 1-3

Dyspnea in an older male Golden Retriever with advanced dilated cardiomyopathy and fulminant pulmonary edema. The dog appeared highly anxious, with rapid labored respirations and hypersalivation. Within minutes after this photograph, respiratory arrest occurred, but the dog was resuscitated and lived another 9 months with therapy for heart failure.



FIG 1-4

Severe dyspnea is manifested in this cat by open-mouth breathing, infrequent swallowing (drooling saliva), and reluctance to lie down. Note also the dilated pupils associated with heightened sympathetic tone.

pleural effusion or other pleural space disease (e.g., pneumothorax) generally causes exaggerated respiratory motions as an effort to expand the collapsed lungs. It is important to note whether the respiratory difficulty is more intense during a particular phase of respiration. Prolonged, labored inspiration is usually associated with upper airway disorders (obstruction), whereas prolonged expiration occurs with lower airway obstruction or pulmonary infiltrative disease (including edema). Animals with severely compromised ventilation may refuse to lie down; they stand or sit with elbows abducted to allow maximal rib expansion, and they resist being positioned in lateral or dorsal recumbency (orthopnea). Cats with dyspnea often crouch in a sternal position with elbows abducted. Open-mouth breathing is usually a sign of severe respiratory distress in cats (Fig. 1-4). The

increased respiratory rate associated with excitement, fever, fear, or pain can usually be differentiated from dyspnea by careful observation and physical examination.

### **MUCOUS MEMBRANES**

Mucous membrane color and capillary refill time (CRT) are used to evaluate peripheral perfusion. The oral mucosa is usually assessed, but caudal mucous membranes (prepuce or vagina) also can be evaluated. The CRT is assessed by applying digital pressure to blanch the membrane; color should return within 2 seconds. Slower refill times occur as a result of dehydration and other causes of decreased cardiac output because of high peripheral sympathetic tone and vasoconstriction. Pale mucous membranes result from anemia or peripheral vasoconstriction. The CRT is normal in anemic animals unless hypoperfusion is also present. However, the CRT can be difficult to assess in severely anemic animals because of the lack of color contrast. The color of the caudal membranes should be compared with that of the oral membranes in polycythemic cats and dogs for evidence of differential cyanosis. If the oral membranes are pigmented, the ocular conjunctiva can be evaluated. Box 1-4 outlines causes for abnormal mucous membrane color. Petechiae in the mucous membranes may be noticed in dogs and cats with platelet disorders (see Chapter 87). In addition, oral and ocular mucous membranes are often areas where icterus (jaundice) is first detected. A yellowish cast to these membranes should prompt further evaluation for hemolysis (see Chapter 83) or hepatobiliary disease (see Chapter 35).

### **JUGULAR VEINS**

Systemic venous and right heart filling pressures are reflected at the jugular veins. These veins should not be distended when the animal is standing with its head in a normal position (jaw parallel to the floor). Persistent jugular vein distention occurs in patients with right-sided CHF (because of high right heart filling pressure), external compression of the cranial vena cava, or jugular vein or cranial vena cava thrombosis (Fig. 1-5).

Jugular pulsations extending higher than one third of the way up the neck from the thoracic inlet also are abnormal. Sometimes the carotid pulse wave is transmitted through adjacent soft tissues, mimicking a jugular pulse in thin or excited animals. To differentiate a true jugular pulse from carotid transmission, the jugular vein is occluded lightly below the area of the visible pulse. If the pulse disappears, it is a true jugular pulsation; if the pulse continues, it is being transmitted from the carotid artery. Jugular pulse waves are related to atrial contraction and filling. Visible pulsations occur in animals with tricuspid insufficiency (after the first heart sound, during ventricular contraction), conditions causing a stiff and hypertrophied right ventricle (just before the first heart sound, during atrial contraction), or arrhythmias that cause the atria to contract against closed AV valves (so-called cannon "a" waves). Specific causes of jugular vein distention and/or pulsations are listed in Box 1-5. Impaired right ventricular filling, reduced pulmonary blood flow, or



BOX 1-4

Abnormal Mucous Membrane Color

### Pale Mucous Membranes

Anemia

Poor cardiac output/high sympathetic tone

### Injected, Brick-Red Membranes

Polycythemia (erythrocytosis)

Sepsis

Excitement

Other causes of peripheral vasodilation

### Cyanotic Mucous Membranes\*

Pulmonary parenchymal disease

Airway obstruction

Pleural space disease

Pulmonary edema

Right-to-left shunting congenital cardiac defect

Hypoventilation

Shock

Cold exposure

Methemoglobinemia

### **Differential Cyanosis**

Reversed patent ductus arteriosus (head and forelimbs receive normally oxygenated blood, but caudal part of body receives desaturated blood via the ductus, which arises from the descending aorta)

### **Icteric Mucous Membranes**

Hemolysis

Hepatobiliary disease

Biliary obstruction

tricuspid regurgitation can cause a positive hepatojugular reflux even in the absence of jugular distension or pulsations at rest. To test for this reflux, firm pressure is applied to the cranial abdomen while the animal stands quietly. This transiently increases venous return. Jugular distention that persists while abdominal pressure is applied constitutes a positive (abnormal) tests. Normal animals have little to no change in the jugular vein.

### **ARTERIAL PULSES**

The strength and regularity of the peripheral arterial pressure waves and the pulse rate are assessed by palpating the femoral or other peripheral arteries (Box 1-6). Subjective evaluation of pulse strength is based on the difference between the systolic and diastolic arterial pressures (the pulse pressure). When the difference is wide, the pulse feels strong on palpation; abnormally strong pulses are termed *hyperkinetic*. When the pressure difference is small, the pulse feels weak (hypokinetic). If the rise to maximum systolic

<sup>\*</sup> Anemic animals may not appear cyanotic even with marked hypoxemia because 5 g of desaturated hemoglobin per decaliter of blood is necessary for visible cyanosis.



FIG 1-5
Prominent jugular vein distention is seen in this cat with signs of right-sided congestive heart failure from dilated cardiomyopathy.



BOX 1-5

Causes of Jugular Vein Distention/Pulsation

### Distention Alone

Pericardial effusion/tamponade
Right atrial mass/inflow obstruction
Dilated cardiomyopathy
Cranial mediastinal mass
Jugular vein/cranial vena cava thrombosis

### Pulsation ± Distention

Tricuspid insufficiency of any cause (degenerative, cardiomyopathy, congenital, secondary to diseases causing right ventricular pressure overload)

Pulmonic stenosis
Heartworm disease
Pulmonary hypertension
Ventricular premature contractions
Complete (third-degree) heart block
Constrictive pericarditis
Hypervolemia

arterial pressure is prolonged, as with severe subaortic stenosis, the pulse also feels weak (*pulsus parvus et tardus*). Both femoral pulses should be palpated and compared; absence of pulse or a weaker pulse on one side may be caused by thromboembolism. Femoral pulses can be difficult to palpate in cats, even when normal. Often an elusive pulse can be found by gently working a fingertip toward the cat's femur in the area of the femoral triangle, where the femoral artery enters the leg between the dorsomedial thigh muscles.



BOX 1-6

### Abnormal Arterial Pulses

### **Weak Pulses**

Dilated cardiomyopathy (Sub)aortic stenosis Pulmonic stenosis Shock Dehydration

### Strong Pulses

Excitement Hyperthyroidism Fever Hypertrophic cardiomyopathy

### Very Strong, Bounding Pulses

Patent ductus arteriosus Fever/sepsis Severe aortic regurgitation

The femoral arterial pulse rate should be evaluated simultaneously with the direct heart rate, which is obtained by chest wall palpation or auscultation. Fewer femoral pulses than heartbeats constitutes a pulse deficit. Various cardiac arrhythmias induce pulse deficits by causing the heart to beat before adequate ventricular filling has occurred. Consequently, minimal or even no blood is ejected for those beats and a palpable pulse is absent. Other arterial pulse variations occur occasionally. Alternately weak then strong pulsations can result from severe myocardial failure (pulsus alternans) or from a normal heartbeat alternating with a premature beat (bigeminy), which causes reduced ventricular filling and ejection. An exaggerated decrease in systolic arterial pressure during inspiration occurs in association with cardiac tamponade; a weak arterial pulse strength (pulsus paradoxus) may be detected during inspiration in those patients.

### **PRECORDIUM**

The precordium is palpated by placing the palm and fingers of each hand on the corresponding side of the animal's chest wall over the heart. Normally the strongest impulse is felt during systole over the area of the left apex (located at approximately the fifth intercostal space near the costochondral junction). Cardiomegaly or a space-occupying mass within the chest can shift the precordial impulse to an abnormal location. Decreased intensity of the precordial impulse can be caused by obesity, weak cardiac contractions, pericardial effusion, intrathoracic masses, pleural effusion, or pneumothorax. The precordial impulse should be stronger on the left chest wall than on the right. A stronger right precordial impulse can result from right ventricular hypertrophy or displacement of the heart into the right hemithorax by a mass lesion, lung atelectasis, or chest deformity. Very loud cardiac murmurs cause palpable vibrations on the chest wall



FIG 1-6
Abdominal distention in this young Neapolitan Mastiff is caused by ascites from right heart failure. The dog had congenital tricuspid valve dysplasia with severe regurgitation.

known as a *precordial thrill*. This feels like a buzzing sensation on the hand. A precordial thrill is usually localized to the area of maximal intensity of the murmur.

# EVALUATION FOR FLUID ACCUMULATION

Right-sided CHF promotes abnormal fluid accumulation within body cavities (Fig. 1-6; see also Fig. 9-3) or, usually less noticeably, in the subcutis of dependent areas. Palpation and ballottement of the abdomen, palpation of dependent areas, and percussion of the chest in the standing animal are used to detect effusions and subcutaneous edema. Fluid accumulation secondary to right-sided heart failure is usually accompanied by abnormal jugular vein distention and/or pulsations, unless the animal's circulating blood volume is diminished by diuretic use or other cause. Hepatomegaly and/or splenomegaly may also be noted in cats and dogs with right-sided heart failure.

### **AUSCULTATION**

Thoracic auscultation is used to identify normal heart sounds, determine the presence or absence of abnormal sounds, assess heart rhythm and rate, and evaluate pulmonary sounds. Heart sounds are created by turbulent blood flow and associated vibrations in adjacent tissue during the cardiac cycle. Although many of these sounds are too low in frequency and/or intensity to be audible, others can be heard with the stethoscope or even palpated. Heart sounds are classified as transient sounds (those of short duration) and cardiac murmurs (longer sounds occurring during a normally silent part of the cardiac cycle). Cardiac murmurs and transient sounds are described using general characteristics of sound: frequency (pitch), amplitude of vibrations (intensity/loudness), duration, and quality (timbre). Sound quality is affected by the physical characteristics of the vibrating structures.

Because many heart sounds are difficult to hear, a cooperative animal and a quiet room are important during aus-



**FIG 1-7**During cardiac auscultation, respiratory noise and purring can be decreased or eliminated by gently placing a finger over one or both nostrils for brief periods of time.

cultation. The animal should be standing, if possible, so that the heart is in its normal position. Panting in dogs is discouraged by holding the animal's mouth shut. Respiratory noise can be decreased further by placing a finger over one or both nostrils for a short time. Purring in cats may be stopped by holding a finger over one or both nostrils (Fig. 1-7), waving an alcohol-soaked cotton ball near the cat's nose, or turning on a water faucet near the animal. Various other artifacts can interfere with auscultation, including respiratory clicks, air movement sounds, shivering, muscle twitching, hair rubbing against the stethoscope (crackling sounds), gastrointestinal sounds, and extraneous room noises.

The traditional stethoscope has both a stiff, flat diaphragm and a bell on the chestpiece. The diaphragm, when applied firmly to the chest wall, allows better auscultation of higher-frequency heart sounds than those of low frequency. The bell, applied lightly to the chest wall, facilitates auscultation of lower-frequency sounds such as S<sub>3</sub> and S<sub>4</sub> (see the following section on Gallop Sounds). Some stethoscopes have a single-sided chestpiece that is designed to function as a diaphragm when used with firm pressure and as a bell when used with light pressure. Ideally the stethoscope should have short double tubing and comfortable eartips. The binaural eartubes should be angled rostrally to align with the examiner's ear canals (Fig. 1-8).

Both sides of the chest should be carefully auscultated, with special attention to the valve areas (Fig. 1-9). The stethoscope is moved gradually to all areas of the chest. The examiner should concentrate on the various heart sounds, correlating them to the events of the cardiac cycle, and listen for any abnormal sounds in systole and diastole successively. The normal heart sounds ( $S_1$  and  $S_2$ ) are used as a framework for timing abnormal sounds. The point of maximal intensity (PMI) of any abnormal sounds should be located. The examiner should focus on cardiac auscultation separately from pulmonary auscultation because full assimilation of sounds from both systems simultaneously is unlikely. Pulmonary auscultation is described further in Chapter 20.

### **Transient Heart Sounds**

The heart sounds normally heard in dogs and cats are  $S_1$  (associated with closure and tensing of the AV valves and associated structures at the onset of systole) and  $S_2$  (associated with closure of the aortic and pulmonic valves following ejection). The diastolic sounds ( $S_3$  and  $S_4$ ) are not audible in normal dogs and cats. Fig. 1-10 correlates the hemodynamic events of the cardiac cycle with the ECG and timing of the heart sounds. It is important to understand these events and identify the timing of systole (between  $S_1$  and  $S_2$ ) and diastole (after  $S_2$  until the next  $S_1$ ) in the animal. The precordial impulse occurs just after  $S_1$  (systole), and the arterial pulse between  $S_1$  and  $S_2$ .

Sometimes the first  $(S_1)$  and/or second  $(S_2)$  heart sounds are altered in intensity. A loud  $S_1$  may be heard in dogs and cats with a thin chest wall, high sympathetic tone, tachycar-



FIG 1-8

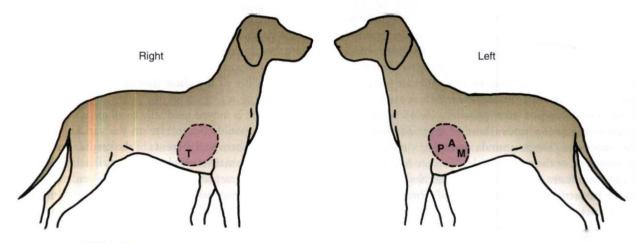
Note the angulation of the stethoscope binaurals for optimal alignment with the clinician's ear canals (Top of picture is rostral). The flat diaphragm of the chestpiece is facing left, and the concave bell is facing right.

dia, systemic arterial hypertension, or shortened PR intervals. A muffled  $S_1$  can result from obesity, pericardial effusion, diaphragmatic hernia, dilated cardiomyopathy, hypovolemia/poor ventricular filling, or pleural effusion. A split or sloppy-sounding  $S_1$  may be normal, especially in large dogs, or it may result from ventricular premature contractions or an intraventricular conduction delay. The intensity of  $S_2$  is increased by pulmonary hypertension (for example, from heartworm disease, a congenital shunt with Eisenmenger's physiology, or cor pulmonale). Cardiac arrhythmias often cause variation in the intensity (or even absence) of heart sounds.

Normal physiologic splitting of  $S_2$  can be heard in some dogs because of variation in stroke volume during the respiratory cycle. During inspiration, increased venous return to the right ventricle tends to delay closure of the pulmonic valve, while reduced filling of the left ventricle accelerates aortic closure. Pathologic splitting of  $S_2$  can result from delayed ventricular activation or prolonged right ventricular ejection secondary to ventricular premature beats, right bundle branch block, a ventricular or atrial septal defect, or pulmonary hypertension.

### **Gallop Sounds**

The third  $(S_3)$  and fourth  $(S_4)$  heart sounds occur during diastole (see Fig. 1-10) and are not normally audible in dogs and cats. When an  $S_3$  or  $S_4$  sound is heard, the heart may sound like a galloping horse, hence the term gallop rhythm. This term can be confusing because the presence or absence of an audible  $S_3$  or  $S_4$  has nothing to do with the heart's rhythm (i.e., the origin of cardiac activation and the intracardiac conduction process). Gallop sounds are usually heard best with the bell of the stethoscope (or by light pressure applied to a single-sided chestpiece) because they are of lower frequency than  $S_1$  and  $S_2$ . At very fast heart rates, differentiation of  $S_3$  from  $S_4$  is difficult. If both sounds are present, they may be superimposed, which is called a summation gallop.



Approximate locations of various valve areas on chest wall. T, Tricuspid; P, pulmonic; A, aortic; M, mitral.

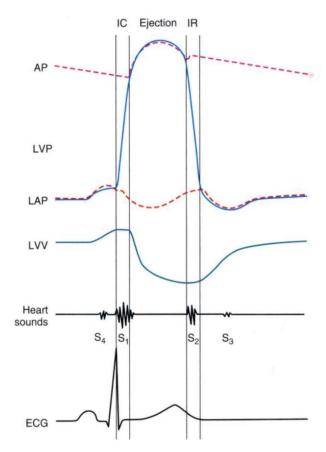


FIG 1-10

Cardiac cycle diagram depicting relationships among great vessel, ventricular and atrial pressures, ventricular volume, heart sounds, and electrical activation. AP, Aortic pressure; ECG, electrocardiogram; IC, isovolumic contraction; IR, isovolumic relaxation; LVP, left ventricular pressure; LAP, left atrial pressure; LVV, left ventricular volume.

The  $S_3$ , also known as an  $S_3$  gallop or ventricular gallop, is associated with low-frequency vibrations at the end of the rapid ventricular filling phase. An audible  $S_3$  in the dog or cat usually indicates ventricular dilation with myocardial failure. The extra sound can be fairly loud or very subtle and is heard best over the cardiac apex. It may be the only auscultable abnormality in an animal with dilated cardiomyopathy. An  $S_3$  gallop may also be audible in dogs with advanced valvular heart disease and congestive failure.

The  $S_4$  gallop, also called an *atrial* or *presystolic gallop*, is associated with low-frequency vibrations induced by blood flow into the ventricles during atrial contraction (just after the P wave of the ECG). An audible  $S_4$  in the dog or cat is usually associated with increased ventricular stiffness and hypertrophy, as with hypertrophic cardiomyopathy or hyperthyroidism in cats. A transient  $S_4$  gallop of unknown significance is sometimes heard in stressed or anemic cats.

### **Other Transient Sounds**

Other brief abnormal sounds are sometimes audible. Systolic clicks are mid-to-late systolic sounds that are usually heard



### TABLE 1-1

### Grading of Heart Murmurs

GRADE	MURMUR
1	Very soft murmur; heard only in quiet
	surroundings after prolonged listening
II	Soft murmur but easily heard
III	Moderate-intensity murmur
IV	Loud murmur but no precordial thrill
٧	Loud murmur with a palpable precordial thrill
VI	Very loud murmur with a precordial thrill; can
	be heard with the stethoscope lifted from the
	chest wall

best over the mitral valve area. These sounds have been associated with degenerative valvular disease (endocardiosis), mitral valve prolapse, and congenital mitral dysplasia; a concurrent mitral insufficiency murmur may be present. In dogs with degenerative valvular disease, a mitral click may be the first abnormal sound noted, with a murmur developing over time. An early systolic, high-pitched ejection sound at the left base may occur in animals with valvular pulmonic stenosis or other diseases that cause dilation of a great artery. The sound is thought to arise from either the sudden checking of a fused pulmonic valve or the rapid filling of a dilated vessel during ejection. Rarely, restrictive pericardial disease causes an audible pericardial knock. This diastolic sound is caused by sudden checking of ventricular filling by the restrictive pericardium; its timing is similar to the S<sub>3</sub>.

### **Cardiac Murmurs**

Cardiac murmurs are described by their timing within the cardiac cycle (systolic or diastolic, or portions thereof), intensity, PMI on the precordium, radiation over the chest wall, quality, and pitch. Systolic murmurs can occur in early (protosystolic), middle (mesosystolic), or late (telesystolic) systole or throughout systole (holosystolic). Diastolic murmurs generally occur in early diastole (protodiastolic) or throughout diastole (holodiastolic). Murmurs at the very end of diastole are termed presystolic. Continuous murmurs begin in systole and extend through S2 into all or part of diastole. Murmur intensity is arbitrarily graded on a I to VI scale (Table 1-1). The PMI is usually indicated by the hemithorax (right or left) and intercostal space or valve area where it is located, or by the terms apex or base. Because murmurs can radiate extensively, the entire thorax, thoracic inlet, and carotid artery areas should be auscultated. The pitch and quality of a murmur relate to its frequency and subjective assessment. "Noisy" or "harsh" murmurs contain mixed frequencies. "Musical" murmurs are of essentially one frequency with its overtones.

Murmurs are also described by phonocardiographic configuration (Fig. 1-11). A holosystolic (plateau-shaped) murmur begins at the time of  $S_1$  and is of fairly uniform

intensity throughout systole. Loud holosystolic murmurs may mask the  $S_1$  and  $S_2$  sounds. AV valve insufficiency and interventricular septal defects commonly cause this type of murmur because turbulent blood flour occurs throughout ventricular systole. A crescendo-decrescendo or diamond-shaped murmur starts softly, builds intensity in midsystole, and then diminishes;  $S_1$  and  $S_2$  can usually be heard clearly

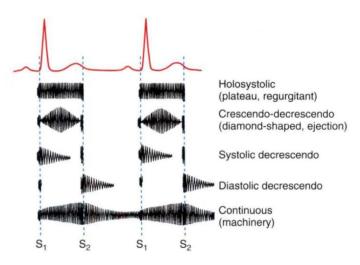


FIG 1-11
The phonocardiographic shape (configuration) as well as the timing of different murmurs are illustrated in this diagram.

before and after the murmur. This type is also called an *ejection murmur* because it occurs during blood ejection, usually because of ventricular outflow obstruction. A decrescendo murmur tapers from its initial intensity over time; it may occur in systole or diastole. Continuous (machinery) murmurs occur throughout systole and diastole.

**Systolic murmurs.** Systolic murmurs can be decrescendo, holosystolic (plateau-shaped), or ejection (crescendo-decrescendo) in configuration. It can be difficult to differentiate these by auscultation alone. But the most important steps toward diagnosis include establishing that a murmur occurs in systole (rather than diastole), determining its PMI, and grading its intensity. Fig. 1-12 depicts the typical PMI of various murmurs over the chest wall.

Functional murmurs usually are heard best over the left heartbase. They are usually soft to moderate in intensity and of decrescendo (or crescendo-decrescendo) configuration. Functional murmurs may have no apparent cardiovascular cause (e.g., "innocent" puppy murmurs) or can result from an altered physiologic state (physiologic murmurs). Innocent puppy murmurs generally disappear by the time the animal is approximately 6 months of age. Physiologic murmurs have been associated with anemia, fever, high sympathetic tone, hyperthyroidism, marked bradycardia, peripheral arteriovenous fistulae, hypoproteinemia, and athletic hearts. Aortic dilation (e.g., with hypertension) and dynamic right ventricular outflow obstruction are other conditions associated with systolic murmurs in cats.

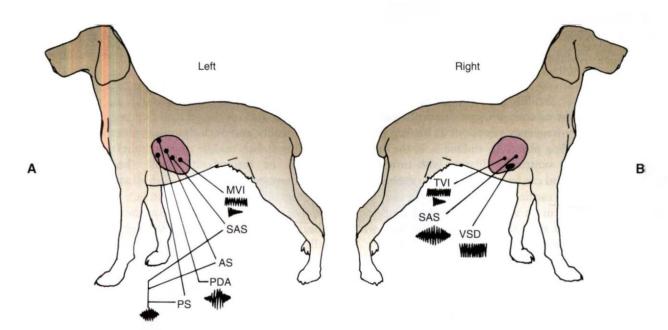


FIG 1-12

The usual point of maximal intensity (PMI) and configuration for murmurs typical of various congenital and acquired causes are depicted on left **(A)** and right **(B)** chest walls. *AS*, aortic (valvular) stenosis; *MVI*, mitral valve insufficiency; *PDA*, patent ductus arteriosus; *PS*, pulmonic stenosis; *SAS*, subaortic stenosis; *TVI*, tricuspid valve insufficiency; *VSD*, ventricular septal defect. (From Bonagura JD, Berkwitt L: Cardiovascular and pulmonary disorders. In Fenner W, editor: *Quick reference to veterinary medicine*, ed 2, Philadelphia, 1991, JB Lippincott.)

The murmur of mitral insufficiency is heard best at the left apex, in the area of the mitral valve. It radiates well dorsally and often to the left base and right chest wall. Mitral insufficiency characteristically causes a plateau-shaped murmur (holosystolic timing), but in its early stages the murmur may be protosystolic, tapering to a decrescendo configuration. Occasionally this murmur has a musical or "whoop-like" quality. With degenerative mitral valve disease, murmur intensity is related to disease severity.

Systolic ejection murmurs are most often heard at the left base and are caused by ventricular outflow obstruction, usually from a fixed narrowing (e.g., subaortic or pulmonic valve stenosis) or dynamic muscular obstruction. Ejection murmurs become louder as cardiac output or contractile strength increases. The subaortic stenosis murmur is heard well at the low left base and also at the right base because the murmur radiates up the aortic arch, which curves toward the right. This murmur also radiates up the carotid arteries and occasionally can be heard on the calvarium. Soft (grade 1-11/VI), nonpathologic systolic ejection (physiologic) murmurs are common in sight hounds and certain other large breeds; these can be related to a large stroke volume (relative aortic stenosis), as well as breed-related left ventricular outflow tract characteristics. The murmur of pulmonic stenosis is best heard high at the left base. Relative pulmonic stenosis occurs with greatly increased flow through a structurally normal valve (e.g., with a large left-to-right shunting atrial or ventricular septal defect).

Most murmurs heard on the right chest wall are holosystolic, plateau-shaped murmurs, except for the subaortic stenosis murmur (above). The tricuspid insufficiency murmur is loudest at the right apex over the tricuspid valve. Its pitch or quality may be noticeably different from a concurrent mitral insufficiency murmur, and it often is accompanied by jugular pulsations. Ventricular septal defects also cause holosystolic murmurs. The PMI is usually at the right sternal border, reflecting the direction of the intracardiac shunt. A large ventricular septal defect may also cause the murmur of relative pulmonic stenosis.

**Diastolic murmurs.** Diastolic murmurs are uncommon in dogs and cats. Aortic insufficiency from bacterial endocarditis is the most common cause, although congenital malformation or degenerative aortic valve disease occasionally occurs. Clinically relevant pulmonic insufficiency is rare but would be more likely in the face of pulmonary hypertension. These diastolic murmurs begin at the time of  $S_2$  and are heard best at the left base. They are decrescendo in configuration and extend a variable time into diastole, depending on the pressure difference between the associated great vessel and ventricle. Some aortic insufficiency murmurs have a musical quality.

**Continuous murmurs.** As implied by the name, continuous (machinery) murmurs occur throughout the cardiac cycle. They indicate that a substantial pressure gradient exists continuously between two connecting areas

(vessels). The murmur is not interrupted at the time of  $S_2$ ; instead, its intensity is often greater at that time. The murmur becomes softer toward the end of diastole, and at slow heart rates it can become inaudible. Patent ductus arteriosus (PDA) is by far the most common cause of a continuous murmur. The PDA murmur is loudest high at the left base above the pulmonic valve area; it tends to radiate cranially, ventrally, and to the right. The systolic component is usually louder and heard well all over the chest. The diastolic component is more localized to the left base in many cases. The diastolic component (and the correct diagnosis) may be missed if only the cardiac apical area is auscultated.

Continuous murmurs can be confused with concurrent systolic ejection and diastolic decrescendo murmurs. But with these so-called "to-and-fro" murmurs, the ejection (systolic) component tapers in late systole and the S<sub>2</sub> can be heard as a distinct sound. The most common cause of to-and-fro murmurs is the combination of subaortic stenosis with aortic insufficiency. Rarely, stenosis and insufficiency of the pulmonic valve cause this type of murmur. Likewise, both holosystolic and diastolic decrescendo murmurs occur occasionally (e.g., with a ventricular septal defect and aortic insufficiency from loss of aortic root support). This also is not considered a true "continuous" murmur.

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# CHAPTER Diagnostic Tests for the Cardiovascular System

# CHAPTER OUTLINE

# CARDIAC RADIOGRAPHY

Cardiomegaly

Cardiac Chamber Enlargement Patterns

Intrathoracic Blood Vessels

Patterns of Pulmonary Edema

#### **ELECTROCARDIOGRAPHY**

Normal ECG Waveforms

Lead Systems

Approach to ECG Interpretation

Sinus Rhythms

**Ectopic Rhythms** 

**Conduction Disturbances** 

Mean Electrical Axis

Chamber Enlargement and Bundle Branch Block

Patterns

ST-T Abnormalities

ECG Manifestations of Drug Toxicity and Electrolyte

Imbalance

Common Artifacts

Ambulatory Electrocardiography

Other Methods of ECG Assessment

#### **ECHOCARDIOGRAPHY**

**Basic Principles** 

Two-Dimensional Echocardiography

M-Mode Echocardiography

Contrast Echocardiography

Doppler Echocardiography

Transesophageal Echocardiography

Three-Dimensional Echocardiography

# OTHER TECHNIQUES

Central Venous Pressure Measurement

**Biochemical Markers** 

Angiocardiography

Cardiac Catheterization

Other Noninvasive Imaging

Pneumopericardiography

Endomyocardial Biopsy

# CARDIAC RADIOGRAPHY

Thoracic radiographs are important for assessing overall heart size and shape, pulmonary vessels, and lung parenchyma, as well as surrounding structures. Both lateral and dorsoventral (DV) or ventrodorsal (VD) views should be obtained. On lateral view, the ribs should be aligned with each other dorsally. On DV or VD views, the sternum, vertebral bodies, and dorsal spinous processes should be superimposed. The views chosen should be used consistently because slight changes in the appearance of the cardiac shadow occur with different positions. For example, the heart tends to look more elongated on the VD view in comparison with that on the DV view. In general, better definition of the hilar area and caudal pulmonary arteries is obtained using the DV view. High kilovoltage peak (kVp) and low milliampere (mA) radiographic technique is recommended for better resolution among soft tissue structures. Exposure is ideally made at the time of peak inspiration. On expiration, the lungs appear denser, the heart is relatively larger, the diaphragm may overlap the caudal heart border, and pulmonary vessels are poorly delineated. Use of exposure times short enough to minimize respiratory motion and proper, straight (not obliquely tilted) patient positioning are important for accurate interpretation of cardiac shape and size and pulmonary parenchyma.

The radiographs should be examined systematically, beginning with assessment of the technique, patient positioning, presence of artifacts, and phase of respiration during exposure. Chest conformation should be considered when evaluating cardiac size and shape in dogs because normal cardiac appearance may vary from breed to breed. The cardiac shadow in dogs with round or barrel-shaped chests has greater sternal contact on lateral view and an oval shape on DV or VD view. In contrast, the heart has an upright, elongated appearance on lateral view and a small, almost circular shape on DV or VD view in narrow- and deep-chested dogs. Because of variations in chest conformation and the influences of respiration, cardiac cycle, and positioning on the apparent size of the cardiac shadow, mild

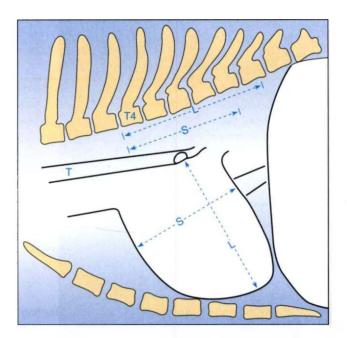


FIG 2-1

Diagram illustrating the vertebral heart score (VHS) measurement method using the lateral chest radiograph. The longaxis (L) and short-axis (S) heart dimensions are transposed onto the vertebral column and recorded as the number of vertebrae beginning with the cranial edge of T4. These values are added to obtain the VHS. In this example, L = 5.8 v, S = 4.6 v; therefore VHS = 10.4 v. T, Trachea. (Modified from Buchanan JW, Bucheler J: Vertebral scale system to measure canine heart size in radiographs, J Am Vet Med Assoc 206:194, 1995.)

cardiomegaly may be difficult to identify. Also, excess pericardial fat may mimic the appearance of cardiomegaly. The cardiac shadow in puppies normally appears slightly large relative to thoracic size compared with that of adult dogs.

The vertebral heart score (VHS) can be used as a means of quantifying the presence and degree of cardiomegaly in dogs and cats, because there is good correlation between body length and heart size regardless of chest conformation. Measurements for the VHS are obtained using the lateral view (Fig. 2-1) in adult dogs and puppies. The cardiac long axis is measured from the ventral border of the left mainstem bronchus to the most ventral aspect of the cardiac apex. This same distance is compared with the thoracic spine beginning at the cranial edge of T4; length is estimated to the nearest 0.1 vertebra. The maximum perpendicular short axis is measured in the central third of the heart shadow; the short axis is also measured in number of vertebrae (to the nearest 0.1) beginning with T4. Both measurements are added to yield the VHS. A VHS between 8.5 to 10.5 vertebrae is considered normal for most breeds. Some variation may exist among breeds; an upper limit of 11 vertebrae may be normal in dogs with a short thorax (e.g., Miniature Schnauzer), whereas an upper limit of 9.5 vertebrae may be normal in dogs with a long thorax (e.g., Dachshund). In some other breeds (e.g.,

Greyhounds), the VHS also can be above the usual reference range.

The cardiac silhouette on lateral view in cats is aligned more parallel to the sternum than in dogs; this parallel positioning may be accentuated in old cats. Radiographic positioning can influence the relative size, shape, and position of the heart because the feline thorax is so flexible. On lateral view the normal cat heart is less than or equal to two intercostal spaces (ICS) in width and less than 70% of the height of the thorax. On DV view the heart is normally no more than one half the width of the thorax. Measurement of VHS is useful in cats also. From lateral radiographs in cats, mean VHS in normal cats is 7.5 vertebrae (range 6.7 to 8.1 v). The mean short axis cardiac dimension taken from DV or VD view, compared with the thoracic spine beginning at T4 on lateral view, was 3.4 to 3.5 vertebrae. An upper limit of normal of 4 vertebrae was identified. In kittens, as in puppies, the relative size of the heart compared with that of the thorax is larger than in adults because of smaller lung volume.

An abnormally small heart shadow results from reduced venous return (e.g., from shock or hypovolemia). The apex appears more pointed and may be elevated from the sternum. Radiographic suggestion of abnormal cardiac size or shape should be considered within the context of the physical examination and other test findings.

#### CARDIOMEGALY

Generalized enlargement of the heart shadow on plain thoracic radiographs may indicate true cardiomegaly or pericardial distention. With cardiac enlargement, the contours of different chambers are usually still evident, although massive right ventricular (RV) and atrial (RA) dilation can cause a round cardiac silhouette. Fluid, fat, or viscera within the pericardium tends to obliterate these contours and create a globoid heart shadow. Common differential diagnoses for cardiac enlargement patterns are listed in Box 2-1.

# CARDIAC CHAMBER ENLARGEMENT PATTERNS

Most diseases that cause cardiac dilation or hypertrophy affect two or more chambers. For example, mitral insufficiency leads to left ventricular (LV) and left atrial (LA) enlargement; pulmonic stenosis causes RV enlargement, a main pulmonary artery bulge, and often RA dilation. For descriptive purposes, however, specific chamber and great vessel enlargements are discussed below. Fig. 2-2 illustrates various patterns of chamber enlargement.

#### **Left Atrium**

The LA is the most dorsocaudal chamber of the heart, although its auricular appendage extends to the left and craniad. An enlarged LA bulges dorsally and caudally on lateral view. There is elevation of the left and possibly right mainstem bronchi; compression of the left mainstem bronchus occurs in patients with severe LA enlargement. In cats the caudal heart border is normally quite straight on lateral view; LA enlargement causes subtle to marked convexity of



# Common Differential Diagnoses for Radiographic Signs of Cardiomegaly

#### Generalized Enlargement of the Cardiac Shadow

Dilated cardiomyopathy
Mitral and tricuspid insufficiency
Pericardial effusion
Peritoneopericardial diaphragmatic hernia
Tricuspid dysplasia
Ventricular or atrial septal defect
Patent ductus arteriosus

#### **Left Atrial Enlargement**

Early mitral insufficiency Hypertrophic cardiomyopathy Early dilated cardiomyopathy (especially Doberman Pinschers) (Sub)aortic stenosis

# Left Atrial and Ventricular Enlargement

Dilated cardiomyopathy
Hypertrophic cardiomyopathy

Mitral insufficiency Aortic insufficiency Ventricular septal defect Patent ductus arteriosus (Sub)aortic stenosis Systemic hypertension Hyperthyroidism

#### Right Atrial and Ventricular Enlargement

Advanced heartworm disease
Chronic, severe pulmonary disease
Tricuspid insufficiency
Pulmonic stenosis
Tetralogy of Fallot
Atrial septal defect
Pulmonary hypertension (with or without reversed shunting congenital defect)
Mass lesion within the right heart

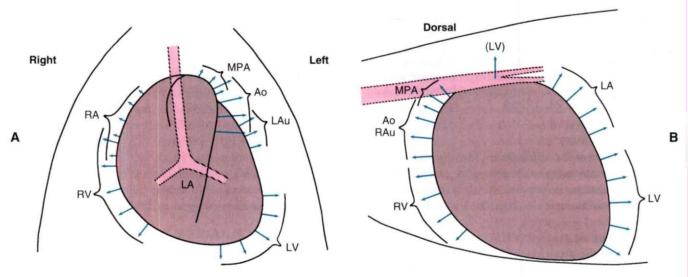


FIG 2-2

Common radiographic enlargement patterns. Diagrams indicating direction of enlargement of cardiac chambers and great vessels in the dorsoventral (A) and lateral (B) views. Ao, Aorta (descending); LA, left atrium; LAu, left auricle; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RAu, right auricle; RV, right ventricle. (Modified from Bonagura JD, Berkwitt L: Cardiovascular and pulmonary disorders. In Fenner W, editor: Quick reference to veterinary medicine, ed 3, Philadelphia, 2000, JB Lippincott.)

the dorsocaudal heart border, with elevation of the mainstem bronchi. On DV or VD view, the mainstem bronchi are pushed laterally and curve slightly around a markedly enlarged LA (sometimes referred to as the "bowed-legged cowboy sign"). A bulge in the 2- to 3-o'clock position of the cardiac silhouette is common in cats and dogs with concurrent left auricular enlargement. Massive LA enlargement sometimes appears as a large, rounded soft tissue opacity superimposed over the LV apical area on DV (VD) view (Fig. 2-3). LA size is influenced by the pressure or volume load imposed, as well as the length of time the overload has been present. For example, mitral regurgitation of slowly increasing severity may cause massive LA enlargement without pulmonary edema if the chamber has had time to dilate at relatively low pressures. Conversely, rupture of chordae tendinae causes acute valvular regurgitation; there can be pulmonary edema with relatively normal LA size because atrial pressure rises quickly.

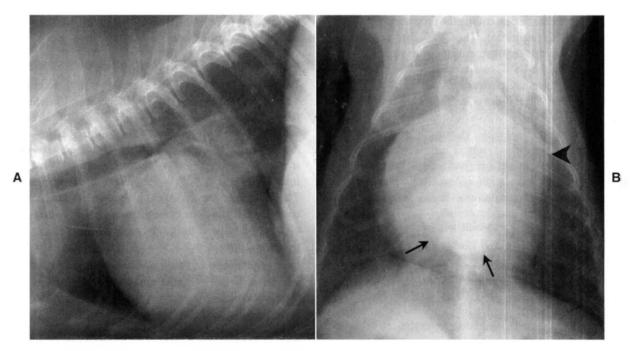


FIG 2-3
Lateral (A) and dorsoventral (B) views from a dog with chronic mitral regurgitation.
Marked left ventricular and atrial enlargement are evident. Dorsal displacement of the carina is seen in A; the caudal edge of the left atrium (arrows), superimposed over the ventricular shadow, and a prominent left auricular bulge (arrowhead) are seen in B.

# Left Ventricle

LV enlargement is manifested on lateral view by a taller cardiac silhouette with elevation of the carina and caudal vena cava. The caudal heart border becomes convex, but cardiac apical sternal contact is maintained. On DV/VD view, rounding and enlargement occur in the 2- to 5-o'clock position. Some cats with hypertrophic cardiomyopathy maintain the apical point; concurrent atrial enlargement creates the classic "valentine-shaped" heart.

#### **Right Atrium**

RA enlargement causes a bulge of the cranial heart border and widening of the cardiac silhouette on lateral view. Tracheal elevation may occur over the cranial portion of the heart shadow. Bulging of the cardiac shadow on DV/VD view occurs in the 9- to 11-o'clock position. The RA is largely superimposed over the RV; although differentiation from RV enlargement is difficult, concurrent enlargement of both chambers is common.

# **Right Ventricle**

RV enlargement (dilation or hypertrophy) usually causes increased convexity of the cranioventral heart border and elevation of the trachea over the cranial heart border on lateral view. With severe RV enlargement and relatively normal left heart size, the apex is elevated from the sternum. The carina and caudal vena cava are also elevated. The degree of sternal contact of the heart shadow is not, by itself, a reliable sign of RV enlargement because of breed variation in

chest conformation. On DV/VD view, the heart tends to take on a reverse-D configuration, especially without concurrent left-sided enlargement. The apex may be shifted leftward, and the right heart border bulges to the right.

# INTRATHORACIC BLOOD VESSELS Great Vessels

The aorta and main pulmonary artery dilate in response to chronic arterial hypertension or increased turbulence (post-stenotic dilation). Subaortic stenosis causes dilation of the ascending aorta. Because of its location within the mediastinum, dilation here is not easily detected, although widening and increased opacity of the dorsocranial heart shadow may be observed. Patent ductus arteriosus causes a localized dilation in the descending aorta just caudal to the arch, which is where the ductus exits; this "ductus bump" is seen on DV or VD view. A prominent aortic arch is more common in cats than dogs. The thoracic aorta of older cats also may have an undulating appearance. Systemic hypertension is a consideration in these cases.

Severe dilation of the main pulmonary trunk (usually associated with pulmonic stenosis or pulmonary hypertension) can be seen as a bulge superimposed over the trachea on lateral radiograph. On DV view in the dog, main pulmonary trunk enlargement causes a bulge in the 1- to 2-o'clock position. In the cat the main pulmonary trunk is slightly more medial and is usually obscured within the mediastinum.

The caudal vena cava (CaVC) normally angles cranioventrally from diaphragm to heart. The width of the CaVC is

approximately that of the descending thoracic aorta, although its size changes with respiration. The CaVC-cardiac junction is pushed dorsally with enlargement of either ventricle. Persistent widening of the CaVC could indicate right ventricular failure, cardiac tamponade, pericardial constriction, or other obstruction to right heart inflow. The following comparative findings suggest abnormal CaVC distention: CaVC/aortic diameter (at same ICS) >1.5; CaVC/length of the thoracic vertebra directly above the tracheal bifurcation >1.3; and CaVC/width of right fourth rib (just ventral to the spine) >3.5. A thin CaVC can indicate hypovolemia, poor venous return, or pulmonary overinflation.

# **Lobar Pulmonary Vessels**

Pulmonary arteries are located dorsal and lateral to their accompanying veins and bronchi. On lateral view, the cranial lobar vessels in the nondependent ("up-side") lung are more ventral and larger than those in the dependent lung. The width of the cranial lobar vessels is measured where they cross the fourth rib in dogs or at the cranial heart border (fourth to fifth rib) in cats. These vessels are normally 0.5 to 1 times the diameter of the proximal one third of the fourth rib. The DV view is best for evaluating the caudal pulmonary vessels. The caudal lobar vessels should be 0.5 to 1 times the width of the ninth (dogs) or tenth (cats) rib at the point of intersection. Four pulmonary vascular patterns are usually described: overcirculation, undercirculation, prominent pulmonary arteries, and prominent pulmonary veins.

An overcirculation pattern occurs when the lungs are hyperperfused, as in left-to-right shunts, overhydration, and other hyperdynamic states. Pulmonary arteries and veins are both prominent; the increased perfusion also generally increases lung opacity. Pulmonary undercirculation is characterized by thin pulmonary arteries and veins, along with increased pulmonary lucency. Severe dehydration, hypovolemia, obstruction to right ventricular inflow, right-sided congestive heart failure, and tetralogy of Fallot can cause this pattern. Some animals with pulmonic stenosis appear to have pulmonary undercirculation. Overinflation of the lungs or overexposure of radiographs also minimizes the appearance of pulmonary vessels.

Pulmonary arteries larger than their accompanying veins indicate pulmonary arterial hypertension. The pulmonary arteries become dilated, tortuous, and blunted, and visualization of the terminal portions is lost. Heartworm disease often causes this pulmonary vascular pattern, as well as patchy to diffuse interstitial pulmonary infiltrates.

Prominent pulmonary veins are a sign of pulmonary venous congestion, usually from left-sided congestive heart failure. On lateral view, the cranial lobar veins are larger and denser than their accompanying arteries and may sag ventrally. Dilated, tortuous pulmonary veins may be seen entering the dorsocaudal aspect of the enlarged LA in dogs and cats with chronic pulmonary venous hypertension. But pulmonary venous dilation is not always visualized in patients with left-sided heart failure. In cats with acute cardiogenic

pulmonary edema, enlargement of both pulmonary veins and arteries can be seen.

#### PATTERNS OF PULMONARY EDEMA

Pulmonary interstitial fluid accumulation increases pulmonary opacity. Pulmonary vessels appear ill-defined, and bronchial walls look thick as interstitial fluid accumulates around vessels and bronchi. As pulmonary edema worsens, areas of fluffy or mottled fluid opacity progressively become more confluent. Alveolar edema causes greater opacity in the lung fields and obscures vessels and outer bronchial walls. The air-filled bronchi appear as lucent, branching lines surrounded by fluid density (air bronchograms). Interstitial and alveolar patterns of pulmonary infiltration can be caused by many pulmonary diseases, as well as by cardiogenic edema (see Chapter 19). The distribution of these pulmonary infiltrates is important, especially in dogs. Cardiogenic pulmonary edema in dogs is classically located in dorsal and perihilar areas and is often bilaterally symmetric. Nevertheless, some dogs develop an asymmetric or concurrent ventral distribution of cardiogenic edema. The distribution of cardiogenic edema in cats is usually uneven and patchy. The infiltrates are either distributed throughout the lung fields or concentrated in the middle zones. Both the radiographic technique and the phase of respiration influence the apparent severity of interstitial infiltrates. Other abnormalities on thoracic radiographs are discussed in the Respiratory Disease section.

#### ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) graphically represents the electrical depolarization and repolarization of cardiac muscle. The ECG provides information on heart rate, rhythm, and intracardiac conduction; it may also suggest the presence of specific chamber enlargement, myocardial disease, ischemia, pericardial disease, certain electrolyte imbalances, and some drug toxicities. But the ECG alone cannot be used to make a diagnosis of congestive heart failure, assess the strength (or even presence) of cardiac contractions, or predict whether the animal will survive an anesthetic or surgical procedure.

# **NORMAL ECG WAVEFORMS**

The normal cardiac rhythm originates in the sinoatrial node and activates the rest of the heart via specialized conduction pathways (Fig. 2-4). The ECG waveforms, P-QRS-T, are generated as heart muscle is depolarized and then repolarized (Fig. 2-5 and Table 2-1). The QRS complex, as a representation of ventricular muscle electrical activation, may not necessarily have each individual Q, R, or S wave components (or variations thereof). The configuration of the QRS complex depends on the lead being recorded as well as the pattern of intraventricular conduction.

# LEAD SYSTEMS

Various leads are used to evaluate the cardiac activation process. The orientation of a lead with respect to the heart

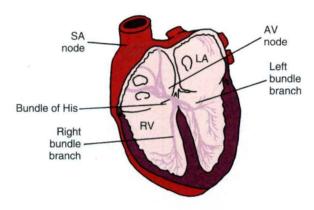


FIG 2-4
Schematic of cardiac conduction system. AV, Atrioventricular; LA, left atrium; RV, right ventricle; SA, sinoatrial. (Modified from Tilley LE: Essentials of canine and feline electrocardiography, ed 3, Philadelphia, 1992, Lea & Febiger.)

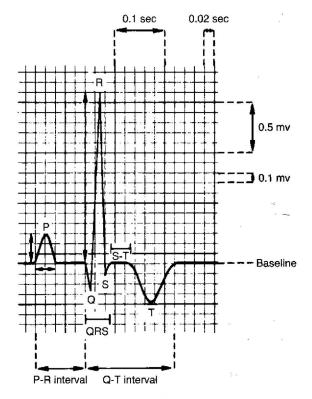


FIG 2-5
Normal canine P-QRS-T complex in lead II. Paper speed is 50 mm/sec; calibration is standard (1 cm = 1 mV). Time intervals (seconds) are measured from left to right; waveform amplitudes (millivolts) are measured as positive (upward) or negative (downward) motion from baseline. (From Tilley LE: Essentials of canine and feline electrocardiography, ed 3, Philadelphia, 1992, Lea & Febiger.)

is called the *lead axis*. Each lead has direction and polarity. If the myocardial depolarization or repolarization wave travels parallel to the lead axis, a relatively large deflection will be recorded. As the angle between the lead axis and the orientation of the activation wave increases toward 90



# TABLE 2-1

Normal Cardiac Waveforms

WAVEFORM	EVENT
P	Activation of atrial muscle; normally is
	positive in leads II and aV <sub>F</sub>
PR interval	Time from onset of atrial muscle
	activation, through conduction over
	the AV node, bundle of His, and
	Purkinje fibers; also called PQ interval
QRS complex	Activation of ventricular muscle; by
	definition, Q is the first negative
	deflection (if present), R the first
	positive deflection, and S is the
	negative deflection after the R wave
J point	End of the QRS complex; junction of
5 po	QRS and ST segment
ST segment	Represents the period between
or oogmon	ventricular depolarization and
	repolarization (correlates with phase 2
	of the action potential)
Twave	Ventricular muscle repolarization
QT interval	
Q1 mervar	Total time of ventricular depolarization
	and repolarization

AV, Atrioventricular.

degrees, the ECG deflection for that lead becomes smaller; it becomes isoelectric when the activation wave is perpendicular to the lead axis. Each lead has a positive and a negative pole or direction. A positive deflection will be recorded in a lead if the cardiac activation wave travels toward the positive pole (electrode) of that lead. If the wave of depolarization travels away from the positive pole, a negative deflection will be recorded in that ECG lead. Both bipolar and unipolar ECG leads are used clinically. A bipolar lead records electrical potential differences between two electrodes on the body surface; the lead axis is oriented between these two points. (Augmented) unipolar leads have a recording electrode (positive) on the body surface. The negative pole of the unipolar leads is formed by "Wilson's central terminal" (V), which is an average of all other electrodes and is analogous to zero.

The standard limb lead system records cardiac electrical activity in the frontal plane (as depicted by a DV/VD radiograph). In this plane, left-to-right and cranial-to-caudal currents are recorded. Fig. 2-6 depicts the six standard frontal leads (hexaxial lead system) overlying the cardiac ventricles. Unipolar chest (precordial) leads "view" the heart from the transverse plane (Fig. 2-7). Box 2-2 lists common ECG lead systems.

#### APPROACH TO ECG INTERPRETATION

Routine ECG recording is usually done with the animal placed on a nonconducting surface in right lateral recumbency. The proximal limbs are parallel to each other and

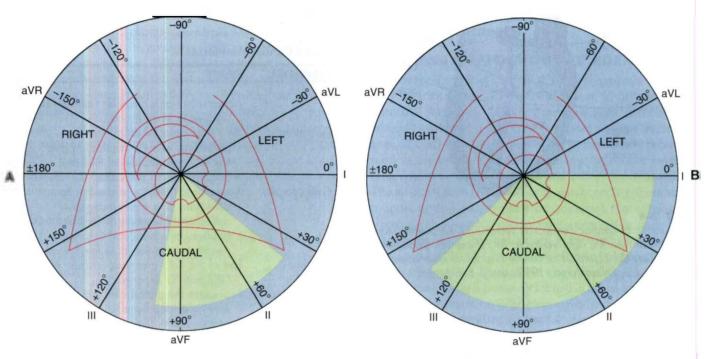


FIG 2-6

Frontal lead system: diagrams of six frontal leads over schematic of left and right ventricles within the thorax. Circular field is used for determining direction and magnitude of cardiac electrical activation. Each lead is labeled at its positive pole. Shaded area represents normal range for mean electrical axis. **A,** Dog. **B,** Cat.

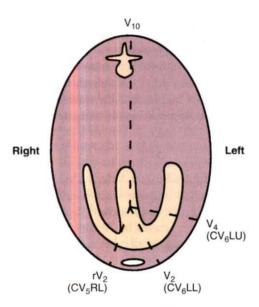


FIG 2-7

Commonly used chest leads seen from cross-sectional view. CV<sub>5</sub>RL is located at right edge of the sternum in fifth intercostal space (ICS), CV<sub>6</sub>LL is near sternum at sixth ICS, CV<sub>6</sub>LU is at costochondral junction at sixth ICS, and V<sub>10</sub> is located near seventh dorsal spinous process.



BOX 2-2

Small Animal ECG Lead Systems

# Standard Bipolar Limb Leads

- I RA (-) compared with LA (+)
- II RA (-) compared with LL (+)
- III LA (-) compared with LL (+)

#### **Augmented Unipolar Limb Leads**

- $aV_R$  RA (+) compared with average of LA and LL (-)
- aV<sub>L</sub> LA (+) compared with average of RA and LL (-)
- aV<sub>F</sub> LL (+) compared with average of RA and LA (-)

#### **Unipolar Chest Leads**

V<sub>1</sub>, rV<sub>2</sub> (CV<sub>5</sub>RL) Fifth right ICS near sternum V<sub>2</sub> (CV<sub>6</sub>LL) Sixth left ICS near sternum

V<sub>2</sub> (CV<sub>6</sub>LL) Sixth left ICS near sternum V<sub>3</sub> Sixth left ICS, equidistant between V<sub>2</sub>

and V₄

V<sub>4</sub> (CV<sub>6</sub>LU) Sixth left ICS near costochondral junction

Spaced as for  $V_3$  to  $V_4$ , continuing

dorsally in sixth left ICS

V<sub>10</sub> Over dorsal spinous process of seventh

thoracic vertebra

#### **Orthogonal Leads**

 $V_5$  and  $V_6$ 

- X Lead I (right to left) in the frontal plane
- Y Lead aV<sub>F</sub> (cranial to caudal) in the midsagittal plane
- Z Lead V<sub>10</sub> (ventral to dorsal) in the transverse plane

RA, Right arm; LA, left arm; LL, left leg; ICS, intercostal space.

perpendicular to the torso. Other body positions may change various waveform amplitudes and affect the calculated mean electrical axis (MEA). However, if only heart rate and rhythm are desired, any recording position can be used. Front limb electrodes are placed at the elbows or slightly below, not touching the chest wall or each other. Rear limb electrodes are placed at the stifles or hocks. With alligator clip or button/plate electrodes, copious ECG paste or (less ideally) alcohol is used to ensure good contact. Communication between two electrodes via a bridge of paste or alcohol or by physical contact should be avoided. The animal is gently restrained in position to minimize movement artifacts. A relaxed and quiet patient produces a better quality tracing. Holding the mouth shut to discourage panting or placing a hand on the chest of a trembling animal may be helpful.

A good ECG recording produces minimal artifact from patient movement, no electrical interference, and a clean baseline. The ECG complexes should be centered and totally contained within the background gridwork so that neither the top nor bottom of the QRS complex is clipped off. If the complexes are too large to fit entirely within the grid, the calibration should be adjusted (e.g., from standard [1 cm = 1 mV] to 1/2 standard [0.5 cm = 1 mV]). The calibration used during the recording must be known to accurately measure waveform amplitude. A calibration square wave (1 mV amplitude) can be inscribed manually during the recording if this is not done automatically. The paper speed and lead(s) recorded also must be evident for interpretation.

A consistent approach to ECG interpretation is recommended. First the paper speed, lead(s) used, and calibration are identified. Then the heart rate, heart rhythm, and MEA are determined. Finally, individual waveforms are measured. The heart rate is the number of complexes (or beats) per minute. This can be calculated by counting the number of complexes in 3 or 6 seconds and then multiplying by 20 or 10, respectively. If the heart rhythm is regular, 3000 divided by the number of small boxes (at paper speed 50 mm/sec) between successive RR intervals equals the instantaneous heart rate. Because variations in heart rate are so common (in dogs especially), determining an estimated heart rate over several seconds is usually more accurate and practical than calculating an instantaneous heart rate.

Heart rhythm is assessed by scanning the ECG for irregularities and identifying individual waveforms. The presence and pattern of P waves and QRS-T complexes are determined. The relationship between the P waves and QRS-Ts is then evaluated. Calipers are often useful for evaluating the regularity and interrelationships of the waveforms. Estimation of MEA is described on p. 28.

Individual waveforms and intervals are usually measured using lead II. Amplitudes are recorded in millivolts and durations in seconds. Only one thickness of the inscribed pen line should be included for each measurement. At 25 mm/sec paper speed, each small (1 mm) box on the ECG gridwork is 0.04 seconds in duration (from left to right). At 50 mm/sec paper speed, each small box equals 0.02 seconds.

A deflection from baseline (up or down) of 10 small boxes (1 cm) equals 1 mV at standard calibration. ECG reference ranges for cats and dogs (Table 2-2) are representative of most normal animals, although complex measurements for some subpopulations can fall outside these ranges. For example, endurance-trained dogs can have ECG measurements that exceed the "normal" range, probably reflecting the training effects on heart size. Such changes in nontrained dogs suggest pathologic cardiac enlargement. Manual frequency filters, available on many ECG machines, can markedly attenuate the recorded voltages of some waveforms when activated, although baseline artifact is reduced. The effects of filtering on QRS amplitude may complicate the assessment for ECG chamber enlargement criteria.

# SINUS RHYTHMS

The normal cardiac rhythm originates in the sinus node and produces the P-QRS-T waveforms previously described. The P waves are positive in caudal leads (II and aVF) and the PQ (or PR) intervals are consistent. Regular sinus rhythm is characterized by less than 10% variation in the timing of the QRS to QRS (or R to R) intervals. Normally the QRS complexes are narrow and upright in leads II and aVF. However, an intraventricular conduction disturbance or ventricular enlargement pattern may cause them to be wide or abnormally shaped.

Sinus arrhythmia is characterized by cyclic slowing and speeding of the sinus rate. This is usually associated with respiration; the sinus rate tends to increase on inspiration and decrease with expiration as a result of fluctuations in vagal tone. There may also be a cyclic change in P-wave configuration ("wandering pacemaker"), with the P waves becoming taller and spiked during inspiration and flatter in expiration. Sinus arrhythmia is a common and normal rhythm variation in dogs. It occurs in resting cats but is not often seen clinically. Pronounced sinus arrhythmia is associated with chronic pulmonary disease in some dogs.

"Brady-" and "tachy-" are modifying terms that describe abnormally slow or fast rhythms, respectively, without identifying intracardiac origin. Both sinus bradycardia and sinus tachycardia are rhythms that originate in the sinus node and are conducted normally; however, the rate of sinus bradycardia is slower than normal for the species, whereas that of sinus tachycardia is faster than normal. Some causes of sinus bradycardia and tachycardia are listed in Box 2-3.

Sinus arrest is absence of sinus activity lasting at least twice as long as the animal's longest expected QRS to QRS interval. An escape complex usually interrupts the resulting pause if sinus activity does not resume in time. Long pauses can cause fainting or weakness. Sinus arrest cannot be differentiated with certainty from sinoatrial (SA) block by the surface ECG. Fig. 2-8 illustrates various sinus rhythms.

# **ECTOPIC RHYTHMS**

Impulses originating from outside the sinus node (ectopic impulses) are abnormal and create an arrhythmia (dysrhythmia). Ectopic impulses are described on the basis of their



TABLE 2-2

# Normal ECG Reference Ranges for Dogs and Cats

DOGS	CATS				
Heart Rate					
70 to 160 beats/min (adults)* to 220 beats/min (puppies)	120 to 240 beats/min				
Mean Electrical Axis (Frontal Plane)					
+40 to +100 degrees	0 to +160 degrees				
Measurements (Lead II) P-wave duration (maximum)					
0.04 sec (0.05 sec, giant breeds)	0.035 to 0.04 sec				
P-wave height (maximum)					
0.4 mV	0.2 mV				
PR interval					
0.06 to 0.13 sec	0.05 to 0.09 sec				
QRS complex duration (maximum)					
0.05 sec (small breeds) 0.06 sec (large breeds)	0.04 sec				
R-wave height (maximum)					
2.5 mV (small breeds) 3 mV (large breeds)†	0.9 mV in any lead; QRS total in any lead <1.2 mV				
ST segment deviation					
<0.2 mV depression <0.15 mV elevation	No marked deviation				
T wave					
Normally <25% of R wave height; can be positive, negative, or biphasic	Maximum 0.3 mV; can be positive (most common), negative, or biphasic				
QT interval duration					
0.15-0.25 (to 0.27) sec; varies inversely with heart rate	0.12 to 0.18 (range 0.07 to 0.2) sec; varies inversely with heart rate				
Chest Leads					
V <sub>1</sub> ; rV <sub>2</sub> : positive T wave V <sub>2</sub> : S wave 0.8 mV maximum; R wave 2.5 mV maximum† V <sub>4</sub> : S wave 0.7 mV maximum; R wave 3 mV maximum†	R wave 1.0 mV maximum				
V <sub>10</sub> : negative QRS; negative T wave (except Chihuahua)	R/Q < 1.0; negative T wave				

Each small box on the ECG paper grid is 0.02 second wide at 50 mm/sec paper speed, 0.04 second wide at 25 mm/sec, and 0.1 mV high at a calibration of 1 cm = 1 mV.

general site of origin (atrial, junctional, supraventricular, ventricular) and their timing (Fig. 2-9). *Timing* refers to whether the impulse occurs earlier than the next expected sinus impulse (premature) or after a longer pause (late or escape). Escape complexes represent activation of a subsidiary pacemaker and function as a rescue mechanism for the

heart. Premature ectopic impulses (complexes) occur singly or in multiples; groups of three or more constitute an episode of tachycardia. Episodes of tachycardia can be brief (paroxysmal tachycardia) or quite prolonged (sustained tachycardia). When one premature complex follows each normal QRS, a bigeminal pattern exists; the origin of the premature

<sup>\*</sup>Range may extend lower for large breeds and higher for toy breeds.
†May be greater in young (under 2 years old), thin, deep-chested dogs.



# Causes of Sinus Bradycardia and Sinus Tachycardia

#### Sinus Bradycardia

Hypothermia Hypothyroidism

Cardiac arrest (before or after)

Drugs (e.g., some tranquilizers, anesthetics, beta-blockers, calcium entry blockers, digoxin)

Increased intracranial pressure

Brainstem lesions

Severe metabolic disease (e.g., hyperkalemia, uremia)

Ocular pressure

Carotid sinus pressure

Other causes of high vagal tone (e.g., airway obstruction)

Sinus node disease

Normal variation (athletic dog)

#### Sinus Tachycardia

Hyperthermia/fever Hyperthyroidism Anemia/hypoxia

Heart failure

Shock

Hypotension

Sepsis

Anxiety/fear

Excitement

Exercise

Pain

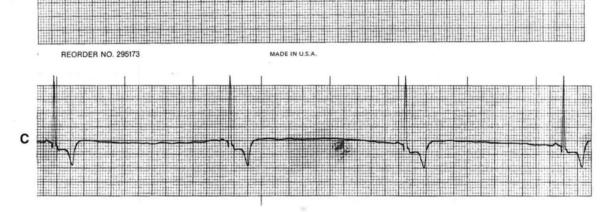
Drugs (e.g., anticholinergics, sympathomimetics)

Toxicities (e.g., chocolate, amphetamines, theophylline)

Electric shock

Other causes of high sympathetic tone

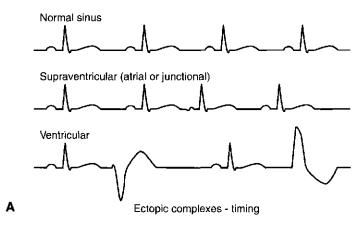


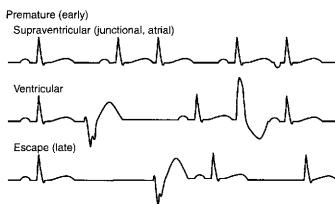


#### FIG 2-8

Sinus rhythms. **A,** Sinus rhythm in normal cat. Lead II, 25 mm/sec. **B,** Sinus arrhythmia with wandering pacemaker in a dog. Note gradual variation in P-wave height associated with respiratory changes in heart rate; this variation is normal in the dog. Lead aVF, 25 mm/sec. **C,** Sinus bradycardia. Lead II, 25 mm/sec, dog.







#### FIG 2-9

В

Diagrams illustrating the appearance of ectopic complexes. Abnormal impulses can originate (A) above the AV node (supraventricular) or from within the ventricles (ventricular). Supraventricular ectopic complexes have a normal-appearing QRS. An abnormal P wave usually precedes a complex originating in atrial tissue; no P wave (or a retrograde P wave in the ST segment—not shown) is common with an impulse originating from the AV junction. Ventricular-origin QRS complexes have a different configuration from the normal sinus QRS. The timing (B) of ectopic complexes refers to whether they appear before the next expected sinus complex (premature or early) or after a longer than expected pause (escape or late).

complexes determines whether the rhythm is described as atrial or ventricular bigeminy. Fig. 2-10 contains examples of supraventricular and ventricular complexes.

# Supraventricular Premature Complexes

Supraventricular premature complexes are impulses that originate above the atrioventricular (AV) node, either in the atria or the AV junctional area. Because they are conducted into and through the ventricles via the normal conduction pathway, their QRS configuration is normal (unless an intraventricular conduction disturbance is also present). Premature complexes arising within the atria are usually preceded by an abnormal P wave (positive, negative, or biphasic configuration) called a P' wave. If an ectopic P' wave occurs before the AV node has completely repolarized, the impulse may not be conducted into the ventricles (an example of physiologic AV block). In some cases, the premature impulse is conducted slowly (prolonged P'Q interval) or with a bundle

#### FIG 2-10

Ectopic complexes and rhythms. A, Atrial premature complexes in an old Cocker Spaniel with mitral insufficiency. Note small negative P waves (arrows) preceding early complexes. Slight increase in QRS size is thought to be related to minor intraventricular conduction delay with prematurity (lead III, 25 mm/sec). B, Short paroxysm of atrial tachycardia (lead II, 25 mm/sec, dog). C, Sustained atrial tachycardia in Irish Setter with mitral stenosis. Note negative, abnormal P waves (lead II, 25 mm/sec). D, Multiform ventricular premature complexes (lead II, 25 mm/sec, dog). **E,** Intermittent paroxysms of ventricular tachycardia demonstrating fusion complex (arrow) (lead II, 25 mm/sec, dog). F, Sustained ventricular tachycardia with several nonconducted P waves (arrows) superimposed (lead aVF, 25 mm/sec, dog). G, Sinus arrhythmia with periods of sinus arrest interrupted by junctional (arrows) and ventricular (arrowheads) escape complexes (lead 11, 25 mm/sec, dog). The differentiation between escape and premature complexes is crucial.

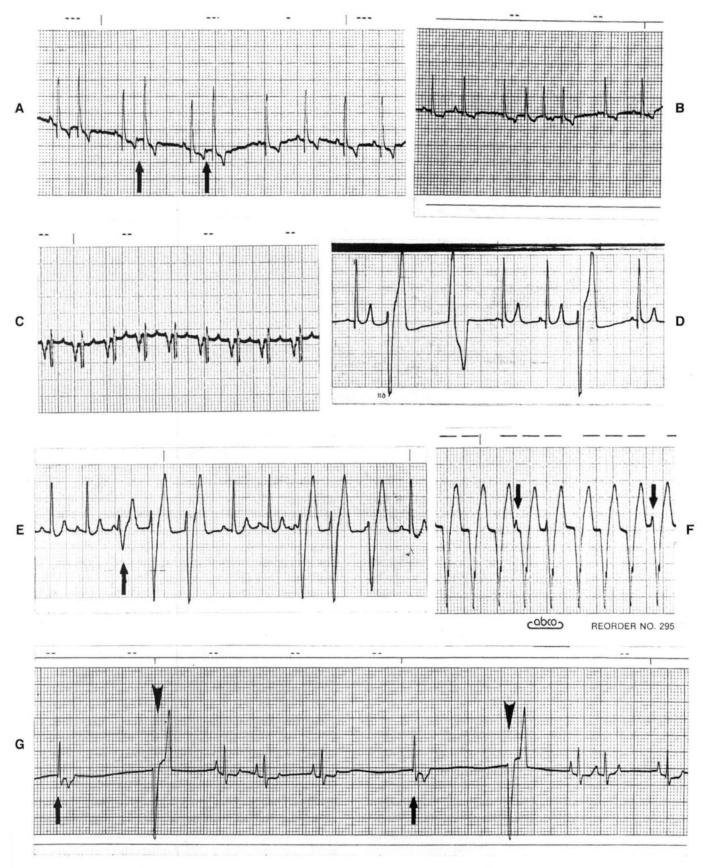


FIG 2-10
For legend, see facing page.

branch block pattern. Although P' waves usually do not precede junctional complexes, retrograde conduction into the atria sometimes causes a negative P' wave to follow, be superimposed on, or even precede the associated QRS complex. If the specific origin of the ectopic complex(es) is unclear, the more general term *supraventricular premature complex* (or *supraventricular tachycardia*) is used. Clinically it is usually more important to determine whether an arrhythmia originates from above the AV node (supraventricular) or below it (ventricular) rather than the more specific localization. Supraventricular premature complexes that also depolarize the sinus node reset the sinus rhythm and create a "noncompensatory pause" (i.e., the interval between the sinus complexes preceding and following the premature complex is less than that of three consecutive sinus complexes).

# Supraventricular Tachycardias

Tachycardias of supraventricular origin often involve a reentrant pathway using the AV node (either within the AV node or using an accessory pathway). A premature supraventricular or ventricular impulse can initiate reentrant supraventricular tachycardia (SVT). During episodes of reentrant SVT in animals with ventricular preexcitation, the PR interval usually normalizes or is prolonged, and retrograde P' waves may be evident. The QRS complexes are of normal configuration unless a simultaneous intraventricular conduction disturbance is present.

Atrial tachycardia is caused by rapid discharge of an abnormal atrial focus or by atrial reentry (repetitive activation caused by conduction of the electrical impulse around an abnormal circuit within the atria). In the dog the atrial activation rate per minute is usually between 260 and 380. The P' waves are often hidden in the QRS-T complexes. Atrial tachycardia can be paroxysmal or sustained. It is usually a regular rhythm unless the rate is too fast for the AV node to conduct every impulse, in which case physiologic AV block and irregular ventricular activation result. A consistent ratio of atrial impulses to ventricular activation (e.g., 2:1 or 3:1 AV conduction) preserves the regularity of this arrhythmia. Sometimes the impulses traverse the AV node but are delayed within the ventricular conduction system, causing a bundle branch block pattern on the ECG. Differentiation from ventricular tachycardia may be difficult in these cases.

#### **Atrial Flutter**

Atrial flutter is caused by a very rapid (usually greater than 400 impulses/min) wave of electrical activation regularly cycling through the atria. The ventricular response may be irregular or regular, depending on the pattern of AV conduction. The ECG baseline consists of "sawtooth" flutter waves that represent the fast, recurrent atrial activation. Atrial flutter is not a stable rhythm; it often degenerates into atrial fibrillation or may convert back to sinus rhythm.

# **Atrial Fibrillation**

This common arrhythmia is characterized by rapid and chaotic electrical activation within the atria. There are no P

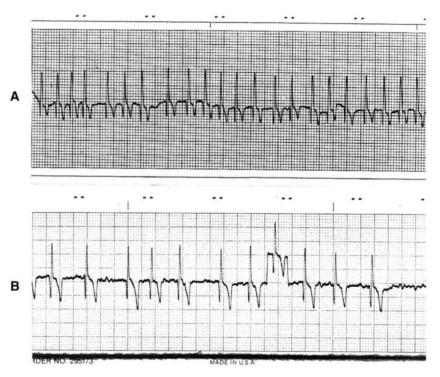
waves on the ECG because there is no uniform atrial depolarization wave. Rather, the baseline usually shows irregular undulations (fibrillation waves). Lack of organized electrical activity prevents meaningful atrial contraction. The AV node, being bombarded by chaotic electrical impulses, conducts as many as possible to the ventricles. Ultimately the (ventricular) heart rate is determined by AV conduction velocity and recovery time, which are influenced by prevailing autonomic tone. Atrial fibrillation (AF) causes an irregular heart rhythm that is often quite rapid (Fig. 2-11). The QRS complexes are usually normal in configuration because intraventricular conduction pathway is usually normal. Minor variation in QRS complex amplitude is common, however, and intermittent or sustained bundle branch blocks can occur. AF tends to be a consequence of severe atrial disease and enlargement in dogs and cats; it is usually preceded by intermittent atrial tachyarrhythmias and perhaps atrial flutter. AF sometimes occurs spontaneously in giant breed dogs without evidence of underlying heart disease ("lone" AF). The heart rate can be normal in these dogs.

# **Ventricular Premature Complexes**

Ventricular premature complexes (VPCs or PVCs) originate below the AV node and do not activate ventricular muscle via the normal ventricular conduction pathway. Therefore their QRS configuration differs from the animal's sinus complexes. Ventricular ectopic complexes are usually wider than sinus-origin complexes because of slower intramuscular conduction. Because VPCs usually are not conducted backward through the AV node into the atria, the sinus rate continues undisturbed; thus the VPC is followed by a "compensatory pause" in the sinus rhythm. When the configuration of multiple VPCs or ventricular tachycardia is consistent in an animal, the complexes are described as being uniform, unifocal, or monomorphic. When the VPCs occurring in an individual have differing configurations, they are said to be multiform or polymorphic. Increased electrical instability may accompany multiform VPCs or tachycardia.

# Ventricular Tachycardia

Ventricular tachycardia consists of a series of VPCs (usually at a rate greater than 100 beats/min). The RR interval is most often regular, although some variation can occur. Nonconducted sinus P waves may be superimposed on or between the ventricular complexes, although they are unrelated to the VPCs because the AV node and/or ventricles are in the refractory period (physiologic AV dissociation). The term capture beat refers to the successful conduction of a sinus P wave into the ventricles uninterrupted by another VPC (i.e., the sinus node has "recaptured" the ventricles). If the normal ventricular activation sequence is interrupted by a VPC, a "fusion" complex can result. A fusion complex represents a melding of the normal QRS configuration and that of the VPC (see Fig. 2-10, E). Fusion complexes are often observed at the onset or end of a paroxysm of ventricular tachycardia; they are preceded by a P wave and shortened PR interval. Identification of P waves (whether conducted or not) or



**FIG 2-11**Atrial fibrillation. **A,** Uncontrolled atrial fibrillation (heart rate 220 beats/min) in a Doberman Pinscher with dilated cardiomyopathy (lead II, 25 mm/sec). **B,** Slower ventricular response rate after therapy in a different Doberman Pinscher with dilated cardiomyopathy showing baseline fibrillation waves. Note lack of P waves and irregular RR intervals. Eighth complex from left superimposed on calibration mark. Lead II, 25 mm/sec.

fusion complexes helps in differentiating ventricular tachycardia from SVT with abnormal (aberrant) intraventricular conduction.

Polymorphic ventricular tachycardia is characterized by QRS complexes that vary in size, polarity, and often rate; sometimes the QRS configuration appears as if it were rotating around the isoelectric baseline. Torsades de pointes is a specific form of polymorphic ventricular tachycardia associated with Q-T interval prolongation.

# **Accelerated Ventricular Rhythm**

Also called *idioventricular tachycardia*, accelerated ventricular rhythm is a ventricular-origin rhythm with a rate of about 60 to 100 beats/min in the dog (perhaps somewhat faster in the cat). Because the rate is slower than true ventricular tachycardia, it is usually a less serious rhythm disturbance. An accelerated ventricular rhythm may appear intermittently during sinus arrhythmia, as the sinus rate decreases; the ventricular rhythm is often suppressed as the sinus rate increases. This is common in dogs recovering from motor vehicle trauma. Often this rhythm disturbance has no deleterious effects, although it could progress to ventricular tachycardia, especially in clinically unstable patients.

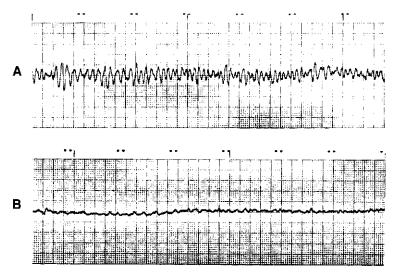
# Ventricular Fibrillation

Ventricular fibrillation is a lethal rhythm that is characterized by multiple reentrant circuits causing chaotic electrical

activity in the ventricles; the ECG consists of an irregularly undulating baseline (Fig. 2-12). The ventricles cannot function as a pump because coordinated mechanical activity cannot occur in the presence of incoordinated electrical activation. Ventricular flutter, which appears as rapid sine-wave activity on the ECG, may precede fibrillation. "Course" ventricular fibrillation (VF) has larger ECG oscillations than "fine" VF.

# **Escape Complexes**

Ventricular asystole is the absence of ventricular electrical (and mechanical) activity. Escape complexes and escape rhythms are a protective mechanism. An escape complex occurs after a pause in the dominant (usually sinus) rhythm. If the dominant rhythm does not resume, the escape focus continues to discharge at its own intrinsic rate. Escape rhythms are usually regular. Escape activity originates from automatic cells within the atria, the AV junction, or the ventricles (see Fig. 2-10, G). Ventricular escape rhythms (idioventricular rhythms) usually have an intrinsic rate less than 40 to 50 beats/min in the dog and 100 beats/min in the cat, although higher ventricular escape rates can occur. Junctional escape rhythms usually range from 40 to 60 beats/min in the dog, with a faster rate expected in the cat. It is important to differentiate escape from premature complexes. Escape activity should never be suppressed with antiarrhythmic drugs.



**FIG 2-12**Ventricular fibrillation. Note chaotic baseline motion and absence of organized waveforms. **A,** Coarse fibrillation; **B,** fine fibrillation. Lead II, 25 mm/sec, dog.

## **CONDUCTION DISTURBANCES**

Abnormal impulse conduction within the atrium can occur at several sites. With sinoatrial (SA) block, impulse transmission from the SA node to the atrial muscle is prevented. Although this cannot reliably be differentiated from sinus arrest on the ECG, with SA block the interval between P waves is a multiple of the normal P to P interval. An atrial, junctional, or ventricular escape rhythm should take over after prolonged sinus arrest or block. Atrial standstill occurs when diseased atrial muscle prevents normal electrical and mechanical function, regardless of sinus node activity; consequently, a junctional or ventricular escape rhythm results and P waves are not seen. Because hyperkalemia interferes with normal atrial function, it can mimic atrial standstill.

# Conduction Disturbances Within the AV Node

Abnormalities of AV conduction can occur from excessive vagal tone, drugs (e.g., digoxin, xylazine, medetomidine, verapamil, and anesthetic agents), and organic disease of the AV node and/or intraventricular conduction system. Three categories of AV conduction disturbances are commonly described (Fig. 2-13). First-degree AV block, the mildest, occurs when conduction from the atria into the ventricles is prolonged. All impulses are conducted, but the PR interval is longer than normal. Second-degree AV block is characterized by intermittent AV conduction; some P waves are not followed by a QRS complex. When many P waves are not conducted, the patient has high-grade second-degree heart block. There are two subtypes of second-degree AV block. Mobitz type I (Wenckebach) is characterized by progressive prolongation of the PR interval until a nonconducted P wave occurs; it is frequently associated with disorders within the AV node itself and/or high vagal tone. Mobitz type II is

characterized by uniform PR intervals preceding the blocked impulse and is thought to be more often associated with disease lower in the AV conduction system (e.g., bundle of His or major bundle branches). An alternative classification of second-degree AV block based on QRS configuration has been described. Patients with type A second-degree block have a normal, narrow QRS configuration; those with type B second-degree block have a wide or abnormal QRS configuration, which suggests diffuse disease lower in the ventricular conduction system. Mobitz type I AV block usually is type A, whereas Mobitz type II frequently is type B. Supraventricular or ventricular escape complexes are common during long pauses in ventricular activation. Third-degree or complete AV block is complete failure of AV conduction; no sinus (or supraventricular) impulses are conducted into the ventricles. Although a regular sinus rhythm or sinus arrhythmia is often evident, the P waves are not related to the QRS complexes, which result from a (usually) regular ventricular escape rhythm.

#### Intraventricular Conduction Disturbances

Abnormal (aberrant) ventricular conduction occurs in association with slowed or blocked impulse transmission in a major bundle branch or ventricular region. The right bundle branch or the left anterior or posterior fascicles of the left bundle branch can be affected singly or in combination. A block in all three major branches results in third-degree (complete) heart block. Activation of the myocardium served by the blocked pathway occurs relatively slowly, from myocyte to myocyte; therefore the QRS complexes appear wide and abnormal (Fig. 2-14). Right bundle branch block (RBBB) is sometimes identified in otherwise normal dogs and cats, although it can occur from disease or distention of the right ventricle. Left bundle branch block (LBBB) is usually related to clinically relevant underlying left ventricular disease. The



#### FIG 2-13

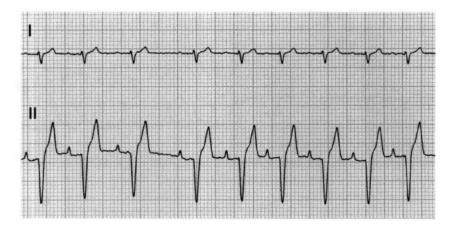
AV conduction abnormalities. **A,** First-degree AV block in a dog with digoxin toxicity (lead aVF, 25 mm/sec). **B,** Second-degree AV block (Wenckebach) in an old cat under anesthesia. Note gradually prolonged PR interval with failed conduction of third (and seventh) P wave(s) followed by an escape complex. The fourth and eighth P waves (arrows) are not conducted because the ventricles are refractory (lead II, 25 mm/sec). **C,** Second-degree AV block in a comatose old dog with brainstem signs and seizures. Note the changing configuration of the P waves (wandering pacemaker) (lead II, 25 mm/sec). **D,** Complete (third-degree) heart block in a Poodle. There is underlying sinus arrhythmia, but no P waves are conducted; a slow ventricular escape rhythm has resulted. Two calibration marks (half-standard, 0.5 cm = 1 mV) are seen. Lead II, 25 mm/sec.

left anterior fascicular block (LAFB) pattern is common in cats with hypertrophic cardiomyopathy.

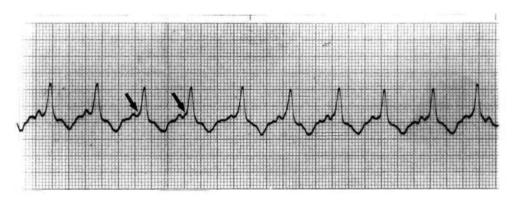
# **Ventricular Preexcitation**

Early activation (preexcitation) of part of the ventricular myocardium can occur when there is an accessory conduction pathway that bypasses the normal slow-conducting AV nodal pathway. Several types of preexcitation and accessory pathways have been described. Most cause a shortened PR interval. Wolff-Parkinson-White (WPW) preexcitation is also characterized by early widening and slurring of the QRS by a so-called delta wave (Fig. 2-15). This pattern occurs because the accessory pathway (Kent's bundle) lies outside

the AV node (extranodal) and allows early depolarization (represented by the delta wave) of a part of the ventricle distant to where normal ventricular activation begins. Other accessory pathways connect the atria or dorsal areas of the AV node directly to the bundle of His. These cause a short PR interval without early QRS widening. Preexcitation can be intermittent or concealed (not evident on ECG). The danger with preexcitation is that a reentrant supraventricular tachycardia can occur using the accessory pathway and AV node (also called AV reciprocating tachycardia). Usually the tachycardia impulses travel into the ventricles via the AV node (antegrade or orthodromic conduction) and then back to the atria via the accessory pathway, but sometimes the



**FIG 2-14** ECG from a dog that developed right bundle branch block and first-degree AV block after doxorubicin therapy. Sinus arrhythmia, Leads I and II, 25 mm/sec, 1 cm = 1 mV.



**FIG 2-15**Ventricular preexcitation in a cat. Note slowed QRS upstroke (delta wave; *arrows*) immediately following each P wave. Lead II, 50 mm/sec, 1 cm = 1 mV.

direction is reversed. Rapid AV reciprocating tachycardia can cause weakness, syncope, congestive heart failure, and death. The presence of the WPW pattern on ECG in conjunction with reentrant supraventricular tachycardia that causes clinical signs characterizes the WPW syndrome.

#### **MEAN ELECTRICAL AXIS**

The mean electrical axis (MEA) describes the average direction of the ventricular depolarization process in the frontal plane. It represents the summation of the various instantaneous vectors that occur from the beginning until the end of ventricular muscle activation. Major intraventricular conduction disturbances and/or ventricular enlargement patterns can shift the average direction of ventricular activation and therefore the MEA. Only the six frontal plane leads are used to determine MEA. Either of the following methods can be used:

1. Find the lead (I, II, III, aVR, aVL, or aVF) with the largest R wave (note: the R wave is a positive deflection). The positive electrode of this lead is the approximate orientation of the MEA.

2. Find the lead (I, II, III, aVR, aVL, or aVF) with the most isoelectric QRS (positive and negative deflections are about equal). Then identify the lead perpendicular to this lead on the hexaxial lead diagram (see Fig. 2-6). If the QRS in this perpendicular lead is mostly positive, the MEA is toward the positive pole of this lead. If the QRS in the perpendicular lead is mostly negative, the MEA is oriented toward the negative pole. If all leads appear isoelectric, the frontal axis is indeterminate. Fig. 2-6 shows the normal MEA range for dogs and cats.

# CHAMBER ENLARGEMENT AND BUNDLE BRANCH BLOCK PATTERNS

Changes in the ECG waveforms can suggest enlargement or abnormal conduction within a particular cardiac chamber. However, enlargement does not always produce these changes. A widened P wave has been associated with LA enlargement (p mitrale); sometimes the P wave is notched as well as wide. Tall, spiked P waves (p pulmonale) can accompany RA enlargement. With atrial enlargement, the usually obscure atrial repolarization (T<sub>a</sub>) wave may be

evident as a baseline shift in the opposite direction of the P wave.

A right-axis deviation and an S wave in lead I are strong criteria for RV enlargement (or RBBB). Other ECG changes can usually be found as well. Three or more of the criteria listed in Box 2-4 are generally present when right ventricular enlargement exists. RV enlargement (dilation or hypertrophy) is usually pronounced if it is evident on the ECG because LV activation forces are normally so dominant. LV dilation and eccentric hypertrophy (see Chapter 3) often increase R-wave voltage in the caudal leads (II and aVF) and widen the QRS. LV concentric hypertrophy inconsistently produces a left-axis deviation.

Conduction block in the major ventricular conduction pathways disturbs the normal activation process and alters QRS configuration. Electrical activation of ventricular muscle regions served by a diseased bundle branch occurs late and progresses slowly. This widens the QRS complex and shifts the terminal QRS orientation toward the area of delayed activation. Box 2-4 and Fig. 2-16 summarize ECG patterns associated with ventricular enlargement or conduction delay. Box 2-5 lists common clinical associations.

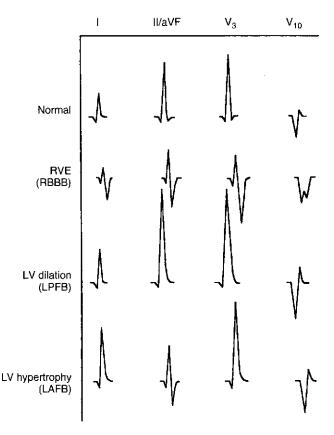


FIG 2-16

Schematic of common ventricular enlargement patterns and conduction abnormalities. ECG leads are listed across top. *LAFB*, left anterior fascicular block; *LPFB*, left posterior fascicular block; *LV*, left ventricular; *RVE*, right ventricular enlargement; *RBBB*, right bundle branch block.

#### Other QRS Abnormalities

Small-voltage QRS complexes sometimes occur. Causes of reduced QRS amplitude include pleural or pericardial effusions, obesity, intrathoracic mass lesions, hypovolemia, and hypothyroidism. Small complexes are occasionally seen in dogs without identifiable abnormalities.

Electrical alternans is an every-other-beat recurring alteration in QRS complex size or configuration. This is most often seen with large volume pericardial effusions (see Chapter 9).

#### ST-T ABNORMALITIES

The ST segment extends from the end of the QRS complex (also called the *J-point*) to the onset of the T wave. In dogs



**BOX 2-4** 

Ventricular Chamber Enlargement and Conduction Abnormality Patterns

#### Normal

Normal mean electrical axis
No S wave in lead I
R wave taller in lead II than in lead I
Lead V<sub>2</sub> R wave larger than S wave

#### Right Ventricular Enlargement

Right-axis deviation
S wave present in lead I
S wave in V<sub>23</sub> larger than R wave or >0.8 mV
Q-S (W shape) in V<sub>10</sub>
Positive T wave in lead V<sub>10</sub> (except Chihuahua breed)

Positive T wave in lead  $V_{10}$  (except Chihuahua breed) Deep S wave in leads II, III, and  $aV_F$ 

#### Right Bundle Branch Block (RBBB)

Same as right ventricular enlargement, with prolonged terminal portion of the QRS (wide, sloppy S wave)

# Left Ventricular Hypertrophy

Left-axis deviation

R wave in lead I taller than R wave in leads II or  $aV_{\text{F}}$  No S wave in lead I

#### Left Anterior Fascicular Block (LAFB)

Same as left ventricular hypertrophy, possibly with wider QRS

# Left Ventricular Dilation

Normal frontal axis

Taller than normal R wave in leads II,  $aV_F$ ,  $V_{2,3}$ 

Widened QRS; slurring and displacement of ST segment and T-wave enlargement may also occur

#### Left Bundle Branch Block (LBBB)

Normal frontal axis

Very wide and sloppy QRS

Small Q wave may be present in leads II, III, and  $aV_F$  (incomplete LBBB)



BOX 2-5

Clinical Associations of ECG Enlargement Patterns

#### Left Atrial Enlargement

Mitral insufficiency (acquired or congenital)
Cardiomyopathies
Patent ductus arteriosus
Subaortic stenosis
Ventricular septal defect

#### **Right Atrial Enlargement**

Tricuspid insufficiency (acquired or congenital) Chronic respiratory disease Interatrial septal defect Pulmonic stenosis

#### Left Ventricular Enlargement (Dilation)

Mitral insufficiency
Dilated cardiomyopathy
Aortic insufficiency
Patent ductus arteriosus
Ventricular septal defect
Subaortic stenosis

#### Left Ventricular Enlargement (Hypertrophy)

Hypertrophic cardiomyopathy Subaortic stenosis

#### **Right Ventricular Enlargement**

Pulmonic stenosis
Tetralogy of Fallot
Tricuspid insufficiency (acquired or congenital)
Severe heartworm disease
Severe pulmonary hypertension (of other cause)

and cats this segment tends to slope into the following T-wave, so clear demarcation is uncommon. Abnormal elevation (>0.15 mV in dogs or 0.1 mV in cats) or depression (>0.2 mV in dogs or >0.1 mV in cats) of the J point and ST segment in leads I, II, or aVF may be significant and can be caused by ischemia and other types of myocardial injury.

Atrial enlargement or tachycardia can cause pseudodepression of the ST segment because of prominent T<sub>a</sub> waves. Other secondary causes of ST segment deviation include ventricular hypertrophy, slowed conduction, and some drugs (e.g., digoxin).

The T wave represents ventricular muscle repolarization; it may be positive, negative, or biphasic in normal cats and dogs. Changes in size, shape, or polarity from previous recordings in a given animal are probably clinically important. Abnormalities of the T wave can be primary (i.e., not related to the depolarization process) or secondary (i.e., related to abnormalities of ventricular depolarization). Secondary ST-T changes tend to be in the opposite direction of the main QRS deflection. Box 2-6 lists some causes of ST-T abnormalities.



#### Causes of ST Segment, T Wave, and QT Abnormalities

#### Depression of J Point/ST Segment

Myocardial ischemia

Myocardial infarction/injury (subendocardial)

Hyperkalemia or hypokalemia

Cardiac trauma

Secondary change (ventricular hypertrophy, conduction disturbance, VPCs)

Digitalis ("sagging" appearance) Pseudodepression (prominent T<sub>a</sub>)

#### Elevation of the J Point/ST Segment

**Pericarditis** 

Left ventricular epicardial injury Myocardial infarction (transmural)

Myocardial hypoxia

Secondary change (ventricular hypertrophy, conduction disturbance, VPCs)

Digoxin toxicity

#### **Prolongation of QT Interval**

Hypocalcemia
Hypokalemia
Quinidine toxicity
Ethylene glycol poisoning
Secondary to prolonged QRS
Hypothermia
Central nervous system abnormalities

# Shortening of QT Interval

Hypercalcemia Hyperkalemia Digitalis toxicity

#### Large T Waves

Myocardial hypoxia
Ventricular enlargement
Intraventricular conduction abnormalities
Hyperkalemia
Metabolic or respiratory diseases
Normal variation

#### Tented T Waves

Hyperkalemia

VPC, Ventricular premature complex.

#### QT Interval

The QT interval represents the total time of ventricular activation and repolarization. This interval varies inversely with average heart rate; faster rates have a shorter QT interval. Autonomic nervous tone, various drugs, and electrolyte disorders influence the duration of the QT interval (see Box 2-6). Inappropriate prolongation of the QT interval may facilitate development of serious reentrant arrhythmias when underlying nonuniformity in ventricular repolariza-

tion exists. Prediction equations for expected QT duration have been derived for normal dogs and cats.

# ECG MANIFESTATIONS OF DRUG TOXICITY AND ELECTROLYTE IMBALANCE

Digoxin, antiarrhythmic agents, and anesthetic drugs often alter heart rhythm and/or conduction either by their direct electrophysiologic effects or by affecting autonomic tone (Box 2-7).

Potassium has marked and complex influences on cardiac electrophysiology. Hypokalemia can increase spontaneous automaticity of cardiac cells, as well as nonuniformly slow repolarization and conduction; these effects predispose to both supraventricular and ventricular arrhythmias. Hypokalemia can cause progressive ST segment depression, reduced T-wave amplitude, and QT interval prolongation. Severe hypokalemia can also increase QRS and P-wave amplitudes and durations. In addition, hypokalemia exacerbates digoxin toxicity and reduces the effectiveness of class I antiarrhyth-

mic agents (see Chapter 4). Hypernatremia and alkalosis worsen the effects of hypokalemia on the heart.

Moderate hyperkalemia actually has an antiarrhythmic effect by reducing automaticity and enhancing uniformity and speed of repolarization. However, rapid or severe increases in serum potassium concentration are arrhythmogenic primarily because they slow conduction velocity and shorten the refractory period. Fig. 2-17 describes the progression of ECG changes as serum potassium concentration rises. The sinus node is relatively resistant to the effects of hyperkalemia and continues to function, although often at a slower rate. Despite progressive atrial muscle unresponsiveness, specialized fibers transmit sinus impulses to the ventricles, producing a "sinoventricular" rhythm. The characteristic "tented" T-wave appearance may be more apparent in some leads than in others and may be of small amplitude. Fig. 2-18 illustrates the ECG effects of severe hyperkalemia and the response to therapy in a dog with Addison's disease. Hypocalcemia, hyponatremia, and acidosis accentuate the ECG changes caused by hyperkalemia,



BOX 2-7

ECG Changes Associated With Electrolyte Imbalance and Selected Drug Adverse Effects/Toxicity

#### Hyperkalemia (see Figs. 2-17, 2-18)

Peaked (tented) ± large T waves

Short QT interval

Flat or absent P waves

Widened QRS

ST segment depression

#### Hypokalemia

ST segment depression Small, biphasic T waves Prolonged QT interval Tachyarrhythmias

# Hypercalcemia

Few effects Short QT interval Prolonged conduction Tachyarrhythmias

#### Hypocalcemia

Prolonged QT interval Tachyarrhythmias

# Digoxin

PR prolongation

Second- (or third-) degree AV block Sinus bradycardia or arrest Accelerated junctional rhythm Ventricular premature complexes Ventricular tachycardia Paroxysmal atrial tachycardia with block

Atrial fibrillation with slow ventricular rate

#### Quinidine/Procainamide

Atropine-like effects
Prolonged QT interval
AV block
Ventricular tachyarrhythmias
Widened QRS complex
Sinus arrest

#### Lidocaine

AV block

Ventricular tachycardia

Sinus arrest

#### **Beta Blockers**

Sinus bradycardia Prolonged PR interval AV block

#### Barbiturates/Thiobarbiturates

Ventricular bigeminy

#### Halothane/Methoxyflurane

Sinus bradycardia

Ventricular arrhythmias (increased sensitivity to catecholamines, especially halothane)

## Medetomidine/Xylazine

Sinus bradycardia Sinus arrest/sinoatrial block AV block

Ventricular tachyarrhythmias (especially with halothane, epinephrine)

AV, Atrioventricular.

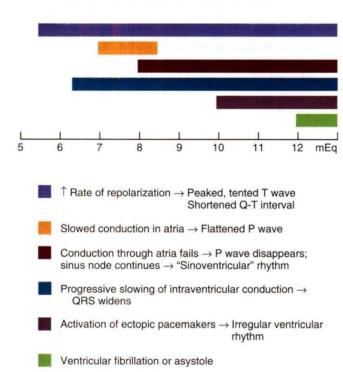


FIG 2-17

Progressive ECG changes that develop with worsening hyperkalemia (scale represents serum  $K^+$  concentration in mEq/L). Although ECG changes correlate poorly with serum  $K^+$  concentration, they accurately reflect cardiac electrophysiologic changes.

whereas hypercalcemia and hypernatremia tend to counteract them.

Marked ECG changes caused by other electrolyte disturbances are uncommon. Severe hypercalcemia or hypocalcemia could have noticeable effects (Table 2-3 on p. 34), but this is rarely seen clinically. Hypomagnesemia has no reported effects on the ECG, but it can predispose to digoxin toxicity and exaggerate the effects of hypocalcemia.

#### **COMMON ARTIFACTS**

Fig. 2-19 on p. 35 illustrates some common ECG artifacts. Electrical interference can be minimized or eliminated by properly grounding the ECG machine; turning off other electrical equipment or lights on the same circuit or having a different person restrain the animal may also help. Other artifacts are sometimes confused with arrhythmias; however, artifacts do not disturb the underlying cardiac rhythm. Conversely, ectopic complexes often disrupt the underlying rhythm and are followed by a T wave. Careful examination for these characteristics usually allows differentiation between intermittent artifacts and arrhythmias.

# **AMBULATORY ELECTROCARDIOGRAPHY**Holter Monitoring

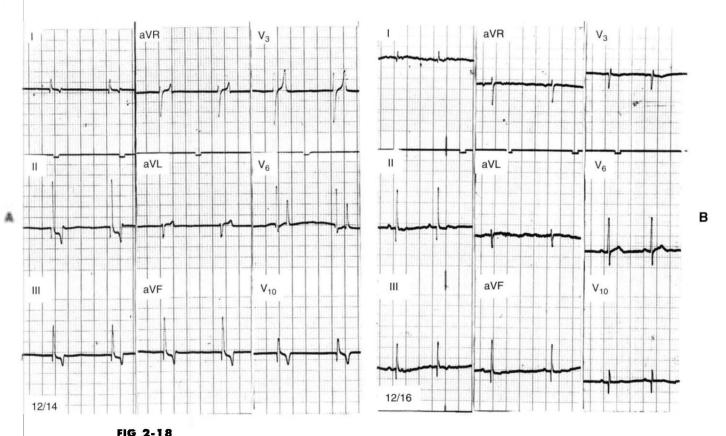
Holter monitoring allows the continuous recording of cardiac electrical activity during normal daily activities (except swimming), strenuous exercise, and sleep. This is useful for detecting and quantifying intermittent cardiac arrhythmias and therefore helps identify cardiac causes of syncope and episodic weakness. Holter monitoring is also used to assess the efficacy of antiarrhythmic drug therapy and to screen for arrhythmias associated with cardiomyopathy or other diseases. The Holter monitor is a small battery-powered digital or analog tape recorder worn by the patient, typically for 24 hours. Two or three ECG channels are recorded from modified chest leads using adhesive patch electrodes. During the recording period, the animal's activities are noted in a patient diary for later correlation with simultaneous ECG events. An event button on the Holter recorder can be pressed to mark the time a syncopal or other episode is witnessed.

The digitized recording is analyzed using computer algorithms that classify the recorded complexes. Evaluation and editing by a trained Holter technician experienced with veterinary recordings are important for accurate analysis. Fully automated computer analysis can result in significant misclassification of QRS complexes and artifacts from dog and cat recordings. A summary report and selected portions of the recording are enlarged and printed for examination by the clinician. Evaluation of a full disclosure print-out of the entire recording is also helpful when compared with the selected ECG strips and the times of clinical signs and/or activities noted in the patient diary (see Suggested Readings for more information). A Holter monitor, hook-up supplies, and analysis can be obtained from some commercial human Holter scanning services, as well as many veterinary teaching hospitals and cardiology referral centers.

Wide variation in heart rate is seen throughout the day in normal animals. In dogs maximum heart rates of up to 300 beats/min have been recorded with excitement or activity. Episodes of bradycardia (<50 beats/min) are common, especially during quiet periods and sleep. Sinus arrhythmia, sinus pauses (sometimes for more than 5 seconds), and occasional second-degree AV block are apparently common in dogs, especially at times when mean heart rate is lower. In normal cats heart rates also vary widely over 24 hours (e.g. from ~70 to ~290 beats/minute. Regular sinus rhythm predominates in normal cats, and sinus arrhythmia is evident at slower heart rates. Ventricular premature complexes occur only sporadically in normal dogs and cats; their prevalence likely increases only slightly with age.

# **Event Recording**

Cardiac event recorders are smaller than typical Holter units and contain a microprocessor with a memory loop that can store a brief period of a single modified chest lead ECG. The event recorder can be worn for periods of a week or so, but it cannot store prolonged, continuous ECG activity. Event recorders are used most often to determine whether episodic weakness or syncope is caused by a cardiac arrhythmia. When an episode is observed, the owner activates the recorder, which then stores the ECG from a predetermined time frame (e.g., from 30 seconds before activation to 30



ECGs recorded in a female Poodle with Addison's disease at presentation (**A**),  $\{K^+ = 10.2; Na^+ = 132 \text{ mEq/L}\}$ , and 2 days later after treatment (**B**),  $\{K^+ = 3.5; Na^+ = 144 \text{ mEq/L}\}$ . Note absence of P waves, accentuated and tented T waves (especially in chest leads), shortened QT interval, and slightly widened QRS complexes in **A** compared with **B**. Leads as marked, 25 mm/sec, 1 cm = 1 mV.

seconds after) for later retrieval and analysis. Implantable (subcutaneous) recording devices have also been used in some veterinary patients and can allow intermittent ECG monitoring over an extended time frame.

# OTHER METHODS OF ECG ASSESSMENT Heart Rate Variability (HRV)

Phasic fluctuations in vagal and sympathetic tone during the respiratory cycle, and also during slower periodic oscillations of arterial blood pressure, influence the variation in time between consecutive heartbeats. HRV refers to the fluctuation of beat-to-beat time intervals around their mean value. HRV is influenced by baroreceptor function as well as by the respiratory cycle and sympathetic/parasympathetic balance. The degree of HRV decreases with severe myocardial dysfunction and heart failure, as well as other causes of increased sympathetic tone. The variation in instantaneous heart rate (R-to-R intervals) can be evaluated as a function of time (time-domain analysis) as well as in terms of the frequency and amplitude of its summed oscillatory components (frequency-domain or power spectral analysis). Frequencydomain analysis allows assessment of the balance between sympathetic and vagal modulation of the cardiovascular system. The potential clinical usefulness of HRV as an indicator of autonomic function, and possibly of prognosis, for veterinary patients is being explored (see Suggested Readings).

# Signal-Averaged Electrocardiography (SAECG)

Digital signal averaging of the ECG provides a means of enhancing ECG signal resolution by discarding random components (noise) so that small-voltage potentials that may occur at the end of the QRS complex and into the early ST segment can be detected. These so-called ventricular late potentials can be found in patients with injured myocardium; they indicate the presence of conditions that predispose to reentrant ventricular tachyarrhythmias. The presence of late potentials on SAECG has been identified in some Doberman Pinschers with ventricular tachycardia and significant ventricular dysfunction, but the sensitivity for predicting risk of ventricular tachycardia is unclear (see Suggested Readings).

#### **ECHOCARDIOGRAPHY**

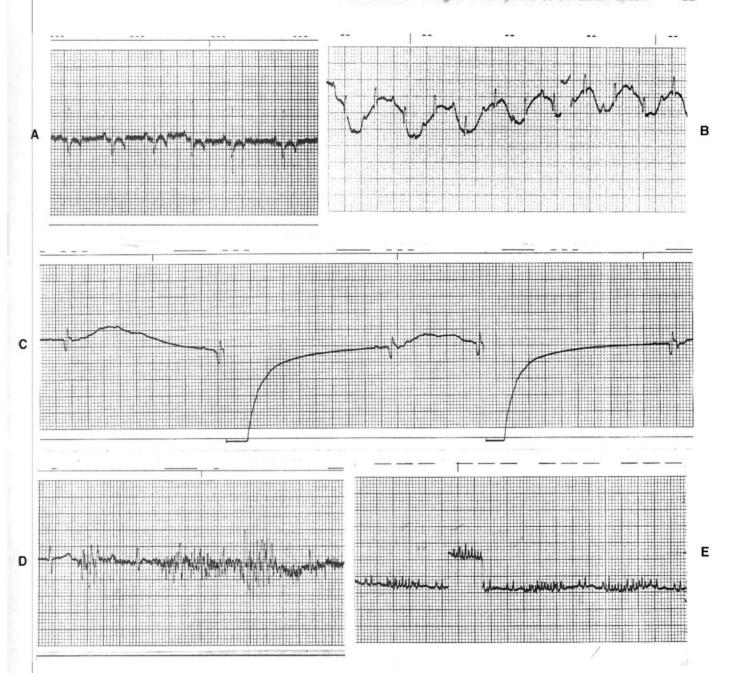
Echocardiography (cardiac ultrasonography) is an important noninvasive tool for imaging the heart and surrounding



Echocardiographic Measurements for Dogs\*

		BODY WEIGHT								M-MODE LA	M-MODE	M-MODE
BREED	N	(kg)	LVID <sub>D</sub> (mm)	LVID <sub>s</sub> (mm)	LVW <sub>D</sub> (mm)	LVW <sub>5</sub> (mm)	IVS <sub>D</sub> (mm)	IVS <sub>s</sub> (mm)	F\$ (%)	(mm)	AO (mm)	LA/AO
Miniature Poodle <sup>(Morrison 192)</sup>	20	3 (1.4-9)	20 (16-28)	10 (8-16)	5 (4-6)	8 (6-10)	-	-	47 (35-57)	12 (8-18)	10 (8-13)	1.2
Beagle <sup>(Crippa '92)</sup>	20	$8.9 \pm 1.5$	26.3 (19.5-33.1)	15.7 (8.9-22.5)	8.2 (4.4-12)	11.4 (7.6-15.2)	6.7 (4.5-8.9)	9.6 (6.6-12.6)	40 (22-58)			
West Highland White Terrier <sup>(Roade '92)</sup>	34	9.4 ± 2.4	27.2 (21.6-32.8)	16.8 (12.8-20.8)	6.7 (4.7-8.7)	9.8 (6.8-12.8)	7.2 (4.6-9.8)	9.7 (7.1-12.3)	36 (26-46)			
English Cocker Spaniel(Gooding 184)	12	$12.2 \pm 2.25$	33.8 (27,2-40.4)	22.2 (16.6-27.8)	7.9 (5.7-10.1)	-		=	34.3 (25.3-43.3)			
Welsh Corgie <sup>[Morrison '92]</sup>	20	15 (8-19)	32 (28-40)	19 (12-23)	8 (6-10)	12 (8-13)	_	_	44 (33-57)	21 (12-24)	18 (15-22)	1,17
English Pointer(Sisson '91)		19.2 ± 2.8	39.2 (34.4-44)	25.3 (20.5-30.1)	7.1 (5.7-8.5)	11.5 (8.9-14.1)	6.9 (4.7-9.1)	10.6 (8.6-12.6)	35.5 (27.5-43.5)	22.6 (18.6-22.6)	24.1 (20.7-27.5)	0.94 (0.8-1.08)
Afghan Hound Morrison '92		23 (17-36)	42 (33-52)	28 (20-37)	9 (7-11)	12 (9-18)	_	_	33 (24-48)	26 (18-35)	26 (20-34)	1.0
Greyhound <sup>[Poge '93]</sup>		26.6 ± 3.5	44.1 (28.1-50.1)	32.5 (25.5-39.5)	12.1 (8.7-15.5)	15.3 (10.9-19.7)	10.6 (7.2-14)	13.4 (8.2-18.6)	25.3 (12.7-37.9)	, ,		
Boxer <sup>[Herringe '94]</sup>	30	28 ± 7.1	40 (30-50)	26.8	10 (6-14)	15 (11-19)	9 (5-13)	13 (9-1 <i>7</i> )	33 (17-49)	23 (19-27)	22 (18-26)	1.06 (1.04-1.08
Greyhound [Snyder '95]	11	29.1 ± 3.7	46.9 [40.7-53.1]	33.3 (28.1-38.5)	11.6 (8.2-15)	- ' '	13.4 (10-16.8)	_ ` '	28.8 (20.4-37.2)	` ′		·
Galden Retriever <sup>(Marrison 192)</sup>	20	32 (23-41)	45 (37-51)	27 (18-35)	10 (8-12)	15 (10-19)	- ' '	-	39 (27-55)	27 (16-32)	24 (14-27)	1.13
Doberman Pinscher <sup>(Minors 198)</sup>	23	-	40.1 (34.7-45.5)	31.4 (25.9-36.9)	8 (5.6-10.4)	11.2 [8.3-14.1]	-	-	21.7 (14.4-29)			
Doberman Pinscher <sup>(Calvert '86)</sup>	21	36 (31-42)	46.8 (38.5-55.1)	30.8 (24.2-37.4)	9.6 (8.4-10.8)	14.1 (12.4-15.8)	9.6 (8.4-10.8)	14.3 (13-15.6)	34.2 (30.6-37.8)	26.6 [23.6-29.6]	29.9 (25.3-34.5)	0.89
Spanish Mastiff(Bayon '94)	12	52.4 ± 3.3	47.7 (44.9-50.5)	29 (26.8-31.2)	9.7 (8.9-10.5)	15.2 (14.4-16)	9.8 (9-10.6)	15.6 (14.6-16.6)	39.2	28.5 (26.7-30.3)	27.6 [26-29.2]	1.03
Newfoundland <sup>(Koch '96)</sup>		61 (47-69.5)	50 (44-60)	35.5 (29-44)	10 (8-13)	15 (11-16)	11.5 (7-15)	15 (11-20)	30 (22-37)	30 (24-33)	29 (26-33)	1.0 (0.8-1.25)
Great Dane(Koch '96)		62 (52-75)	53 [44-59]	39.5 (34-45)	12.5 (10-16)	16 (11-19)	14.5 (12-16)	16.5 (14-19)	25 (18-36)	33 (28-46)	29.5 (28-34)	1.1 (0.9-1.5)
Irish Wolfhound <sup>(Vollmar '99</sup> ]		65 (43-93)	53.2 (45.2-61.2)	35.4 (29.8-41)	9.8 (6.6-13)	14.9 (10.6-19.2)	9.3 (5.7-12.9)	, ,	34 (25-43)	32.9 (26.1-39.7)	33.1 {27.7-38.7}	0.99
Irish Wolfhound <sup>(Koch '96)</sup>	20	68.5 (50-80)	50 (46-59)	36 (33-45)	10 (9-13)	14 (11-17)	12 (9-14.5)	15 (11-1 <i>7</i> )	28 (20-34)	31 (22-35)	30 (29-31)	1.0 (0.9-1.5)

\*Values expressed as mean  $\pm 2$  standard deviations or {range}. **Comment:** In general, normal FS is considered from 25-40 or 45%, although some healthy athletic dogs have FS between 20% and 25%. Most normal dogs have an EPSS  $\le 6$  mm; may be slightly larger in giant breeds.  $LVID_d$  = left ventricular diameter in diastole;  $LVID_s$  = left ventricular free wall thickness in systole; IVS<sub>3</sub> = interventricular septal thickness in diastole; IVS<sub>5</sub> = interventricular septal thickness in systole; FS = left ventricular fractional shortening.



#### FIG 2-19

Common ECG artifacts. **A,** 60 Hz electrical interference; Lead III, 25 mm/sec, dog. **B,** Baseline movement caused by panting; Lead II, 25 mm/sec, dog. **C,** Respiratory motion artifact; Lead  $V_3$ , 50 mm/sec, dog. **D,** Severe muscle tremor artifact; Lead  $V_3$ , 50 mm/sec, cat. **E,** Intermittent, rapid baseline spikes caused by purring in cat; a calibration mark is seen just left of the center of the strip. Lead aVF, 25 mm/sec.

structures. Anatomic relationships as well as cardiac function can be assessed by evaluating cardiac chamber size, wall thickness, wall motion, valve configuration and motion, and proximal great vessels and other parameters. Pericardial and pleural fluid are easily detected, and mass lesions within and adjacent to the heart can be identified. Echocardiographic examination can usually be performed with minimal or no chemical restraint.

Like other diagnostic modalities, echocardiography is best used within the context of a thorough history, cardiovascular examination, and other appropriate tests. Technical expertise is essential to adequately perform and interpret the echocardiographic examination. The importance of the echocardiographer's skill and understanding of normal and abnormal cardiovascular anatomy and physiology cannot be overemphasized. The ultrasound equipment used as well as

individual patient characteristics also affect the quality of images obtained. Sound waves do not travel well though bone (e.g., ribs) and air (lungs); these structures may preclude good visualization of the entire heart.

# **BASIC PRINCIPLES**

Echocardiography uses pulsed, high-frequency sound waves that are reflected, refracted, and absorbed by body tissue interfaces. Only the reflected portion can be received and processed for display. Transducer frequency, power output, and various processing controls influence the intensity and clarity of the displayed echo images. Three echo modalities are used clinically: M-mode, two-dimensional (2-D, real-time), and Doppler. Each has important applications (described in the subsequent sections).

Sound waves are propagated through soft tissue at a characteristic speed (~1540 m/sec), so the thickness, size, and location of various structures in relation to the origin of the ultrasound beam can be determined at any point in time. Because the intensity of the ultrasound beam decreases as it penetrates into the body (because of beam divergence, absorption, scatter, and reflection of wave energy at tissue interfaces), echoes returning from deeper structures tend to be weaker. When the ultrasound beam (2-D and M-mode) is perpendicular to the imaged structure, stronger echos are returned. Also, greater mismatch in acoustic impedance (which is related to tissue density) between two adjacent tissues produces a more reflective boundary, and stronger echoes result. Very reflective interfaces such as bone/tissue or air/tissue interfere with imaging of weaker echos from deeper tissue interfaces.

Higher frequency ultrasound permits better resolution of small structures because of the beam characteristics of longer near field and lesser far field divergence. However, higher frequencies have less penetrating ability as more energy is absorbed and scattered by the soft tissues. Conversely, a transducer that produces lower frequencies provides greater penetration depth but less well-defined images. Frequencies generally used for small animal echocardiography range from about 3.5 MHz (for large dogs) to >10 MHz (for cats and small dogs). A megahertz (MHz) represents 1,000,000 cycles/sec.

Strongly reflective tissues are referred to as being hyperechoic or of increased echogenicity. Poorly reflecting tissues are hypoechoic; fluid, which does not reflect sound, is anechoic or sonolucent. Tissue behind an area of sonolucency appears hyperechoic because of acoustic enhancement. On the other hand, through-transmission of the ultrasound beam is blocked by a strongly hyperechoic object (such as a rib), and an acoustic shadow (where no image appears) is cast behind the object.

For most echocardiographic examinations, the animal is gently restrained in lateral recumbency; better-quality images are usually obtained when the heart is imaged from the recumbent side. For this the animal is placed on a table or platform with an edge cutout, which allows the echocardiographer to position and manipulate the transducer from the

animal's dependent side. Some animals can be adequately imaged while standing. Shaving a small area of hair over the transducer placement site can improve skin contact and image clarity. Coupling gel is applied to produce air-free contact between skin and transducer. The transducer is placed over the area of the precordial impulse (or other appropriate site), and its position is adjusted to find a good "acoustic window" that allows clear visualization of the heart. The right and left parasternal transducer positions are used most often. Minor adjustment of the animal's forelimb or torso position may be required to obtain a good acoustic window. Once the heart is located, the transducer is angled or rotated and the echocardiograph's controls for factors such as beam strength, focus, and postprocessing parameters are adjusted as necessary to optimize the image. Optimal visualization generally is achieved for 2-D and M-mode studies when the ultrasound beam is perpendicular to the cardiac structures and endocardial surfaces of interest. Image artifacts are common and can mimic a cardiac abnormality. If the suspected lesion can be visualized in more than one imaging plane, it is more likely to be real.

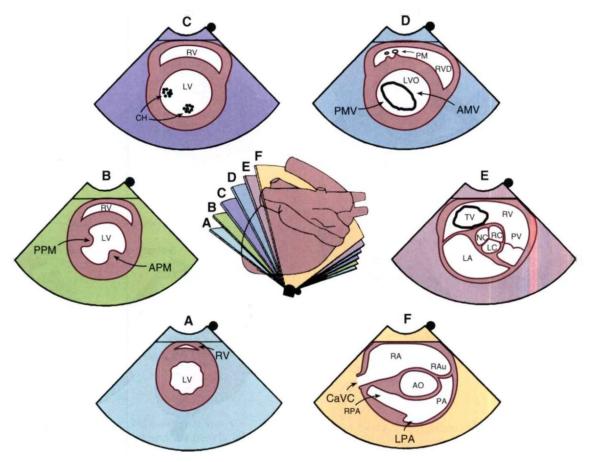
The echocardiographic examination includes carefully obtained M-mode measurements and all standard 2-D imaging planes from both sides of the chest, as well as any other views needed to further evaluate specific lesions. Doppler evaluation provides important additional information (discussed in more detail later). The complete examination can be quite time consuming in some patients. Light sedation is helpful if the animal does not lie quietly. Buprenorphine (0.0075 to 0.01 mg/kg IV) with acepromazine (0.03 mg/kg IV) usually works well for dogs. Butorphanol (0.2 mg/kg IM) with acepromazine (0.1 mg/kg IM) is adequate for many cats, although some require more intense sedation. Acepromazine (0.1 mg/kg IM) followed in 15 minutes by ketamine (2 mg/kg IV) can be used in cats, but this regimen can increase heart rate undesirably.

# TWO-DIMENSIONAL ECHOCARDIOGRAPHY

A plane of tissue (both depth and width) is displayed using 2-D echocardiography. The anatomic changes resulting from various diseases or congenital defects are evident, although actual blood flow is not usually visualized with 2-D or M-mode imaging alone.

# Common 2-D Echocardiographic Views

A variety of planes can be imaged from several chest wall locations. Most standard views are obtained from either the right or left parasternal positions (directly over the heart and close to the sternum). Images are occasionally obtained from subxiphoid (subcostal) or thoracic inlet (suprasternal) positions. Long-axis views are obtained with the imaging plane parallel to the long axis of the heart; short-axis views are perpendicular to this plane (Figs. 2-20 to 2-25). Images are described by the location of the transducer and the imaging plane used (e.g., right parasternal short-axis view, left cranial parasternal long-axis view). 2-D



# FIG 2-20

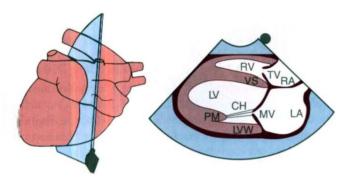
Two-dimensional short-axis echocardiographic views from the right parasternal position. The center diagram indicates the orientation of the ultrasound beam used to image cardiac structures at the six levels shown. Several of these positions guide M-mode beam placement as well as Doppler evaluation of tricuspid and pulmonary flows. Corresponding echo images are shown clockwise from the bottom. **A,** Apex. **B,** Papillary muscle. **C,** Chordae tendineae. **D,** Mitral valve. **E,** Aortic valve. **F,** Pulmonary artery. AMV, Anterior (septal) mitral valve cusp; AO, aorta; APM, anterior papillary muscle; CaVC, caudal vena cava; CH, chordae tendineae; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; LVO, left ventricular outflow tract; PA, pulmonary artery; PM, papillary muscle; PMV, posterior mitral valve cusp; PPM, posterior papillary muscle; PV, pulmonary valve; RA, right atrium; RAu, right auricle; RC, LC, NC, right, left, and noncoronary cusps of aortic valve; RPA, right pulmonary artery; RV, right ventricle; RVO, right ventricular outflow tract; TV, tricuspid valve. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)

imaging allows an overall assessment of cardiac chamber orientation, size and wall thickness. The RV wall is usually about one third of the thickness of the LV free wall and should be no greater than half its thickness. The size of the right atrial and ventricular chambers is subjectively compared with that of the left atrium and ventricle; the right parasternal long axis and left apical 4 chamber views are useful for this. All valves and related structures as well as the great vessels are systematically examined. Any suspected abnormality is scanned in multiple planes to further verify and delineate it.

End diastolic and systolic LV internal dimensions and wall thickness are usually obtained using M-mode, but

appropriately timed 2-D frames can also be used. Several methods can be used to estimate LV volume and wall mass. LA size is better assessed using 2-D rather than M-mode. Several methods for measuring LA size have been described. One is to measure the cranial-caudal diameter (top-to-bottom on screen) at end-systole using a right parasternal long axis four-chamber view. In cats this LA dimension normally is <16 mm; a diameter >19 mm may indicate greater risk for thromboembolism. Because of greater body size variation in dogs, LA dimension is usually compared with the 2-D aortic root diameter measured across the sinuses of Valsalva. A 2-D maximal LA diameter:aortic root ratio between 1.7 to 1.9 is considered normal.

Long-axis 4-chamber view



Long-axis LV outflow view

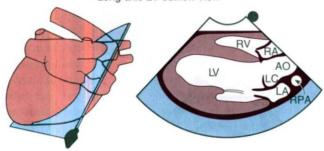


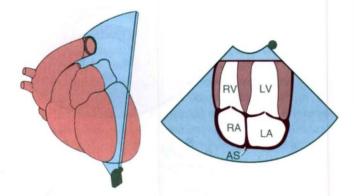
FIG 2-21

Two-dimensional long-axis echocardiographic views from right parasternal position. Each diagram on the left indicates the location of the ultrasound beam as it transects the heart from the right side, resulting in the corresponding echo image on the right. Long-axis four-chamber (left ventricular inflow) view is above. Long-axis view of the left ventricular outflow region is below. AO, Aorta; CH, chordae tendinae; LA, left atrium; LC, left coronary cusp of aortic valve; LV, left ventricle; LVW, left ventricular wall; MV, mitral valve; PM, papillary muscle; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; TV, tricuspid valve; VS, interventricular septum. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)

# M-MODE ECHOCARDIOGRAPHY

This modality provides a one-dimensional view (depth) into the heart. M-mode images represent echos from various tissue interfaces along the axis of the beam (displayed vertically on the screen). These echos, which move during the cardiac cycle, are displayed against time (on the horizontal axis). Thus the "wavy" lines that are seen on these recordings correspond to the positions of particular structures in relation to the transducer as well as to each other at any point in time. Accurate placement of the M-mode beam using a moveable cursor line superimposed on an appropriate 2-D (real-time) image is important. M-mode images usually provide cleaner resolution of cardiac borders than 2-D because of higher sampling rate. Measurements of cardiac dimensions and motion throughout the cardiac cycle are often more accurately obtained from M-mode tracings,

#### 4-chamber (inflow) view



5-chamber (LV outflow) view

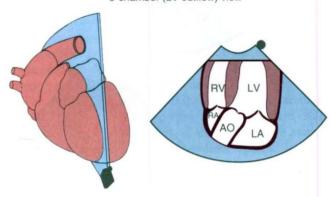


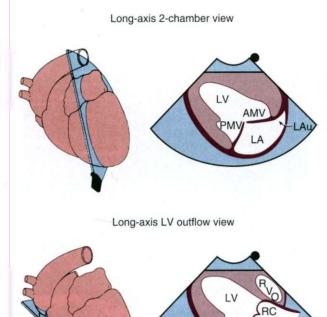
FIG 2-22

Left caudal (apical) parasternal position. Four-chamber view optimized for ventricular inflow is above. Five-chamber view optimized for left ventricular outflow is below. These views provide good Doppler velocity signals from mitral and aortic valve regions. AO, Aorta; AS, interatrial septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)

especially when coupled with a simultaneously recorded ECG (or phonocardiogram). Difficulty in achieving consistent and accurate beam placement for standard measurements and calculations can be a limitation.

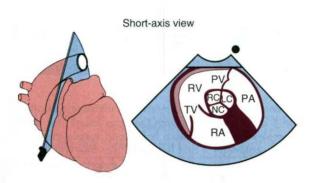
#### M-Mode Views

Standard M-mode views are obtained from the right parasternal transducer position. The M-mode cursor is positioned with 2-D guidance using the right parasternal short-axis view. Precise positioning of the ultrasound beam within the heart (perpendicular to the structures to be measured) and clear endocardial images are essential for accurate M-mode measurements and calculations. For example, papillary muscles within the left ventricle must be avoided when measuring free-wall thickness. Fig. 2-26 illustrates standard M-mode views. In cases in which the M-mode cursor cannot be optimally aligned (e.g., in animals with focal or asymmetric hypertrophy), wall thickness measurements from 2-D images are preferred.



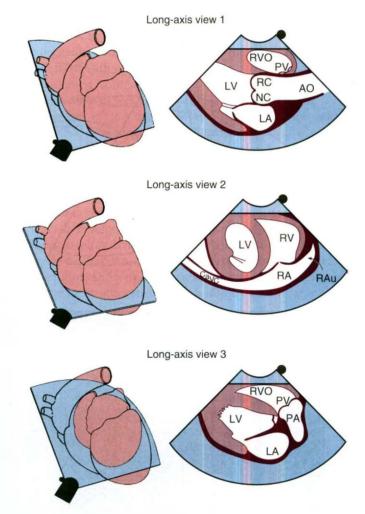
#### FIG 2-23

Left caudal (apical) parasternal 2-dimensional views optimized for left ventricular inflow and left auricle (above) and left ventricular outflow (below). AMV, Anterior (septal) mitral valve cusp; AO, aorta; LA, left atrium; LAu, left auricle; LV, left ventricle; PMV, posterior mitral valve cusp; RC, NC, right and noncoronary cusps of aortic valve; RVO, right ventricular outflow tract. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)



#### FIG 2-24

Left cranial parasternal short-axis view optimized for right ventricular inflow and outflow. This view is useful for Doppler interrogation of tricuspid and pulmonary artery flows. PA, Pulmonary artery; PV, pulmonary valve; RA, right atrium; RC, LC, NC, right, left, and noncoronary cusps of aortic valve; RV, right ventricle; TV, tricuspid valve. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)



#### FIG 2-25

Left cranial parasternal long-axis views optimized for aortic root (above), right atrium and auricle (middle), and right ventricular outflow and main pulmonary artery (below). These views are used to evaluate the heart base and can provide good Doppler signals for tricuspid and pulmonary flows. AO, Aorta; CaVC, caudal vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RAu, right auricle; RC, NC, right and noncoronary cusps of aortic valve; RV, right ventricle; RVO, right ventricular outflow tract. (From Thomas WP et al: Recommendations for standards in transthoracic 2-dimensional echocardiography in the dog and cat, J Vet Intern Med 7:247, 1993.)

# Common Measurements and Normal Values

The standard dimensions measured with M-mode and their timing are also indicated in Fig. 2-26. The leading edge technique is used when possible (i.e., from the edge closest to the transducer [leading edge] of one side of the dimension to the leading edge of the other). In this way, only one endocardial surface is included in the measurement. LV wall and interventricular septal thicknesses, as well as LV chamber dimensions, should be determined at the level of the chordae tendineae, rather than the apex or mitral valve level.

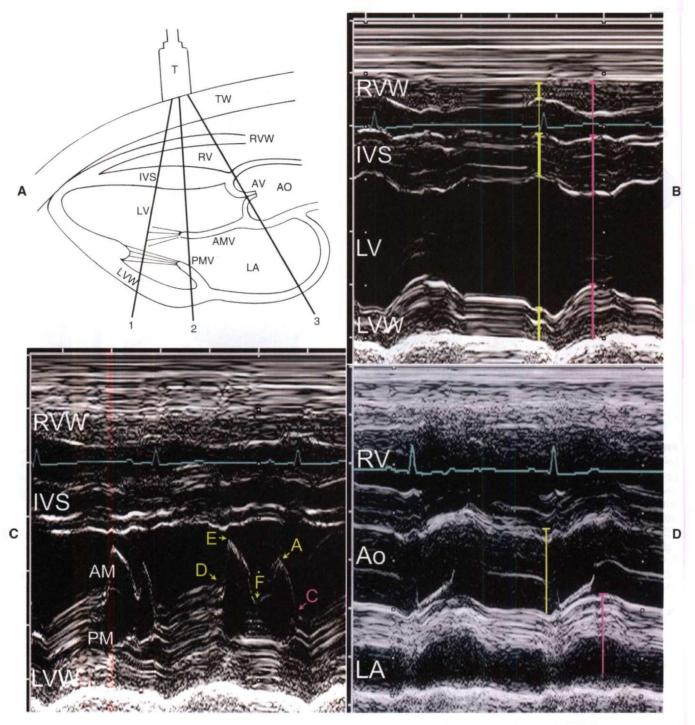


FIG 2-26

Common M-mode views. The diagram (A) indicates the approximate orientation of the one-dimensional ultrasound beam through the heart to achieve the corresponding M-mode images. A lead II ECG is recorded with the echo images for timing within the cardiac cycle. End diastole occurs at the onset of the QRS complex (yellow measure lines); end systole (pink measure lines) is the time when the dimension between the interventricular septum (IVS) and left ventricular free wall (LVW) is smallest. B, Image at the level of the chordae tendineae within the left ventricular lumen (LV), corresponding to cursor line "1" in A. Internal dimensions of the LV are measured from the leading (anterior) edge of the left endocardial wall of the IVS to the leading edge (luminal surface) of the posterior LVW. The thickness of the IVS is measured from the right endocardial surface of the IVS to the leading edge of the left endocardial septal wall at end diastole and end systole; the posterior LVW is measured at the same times from the endocardial surface to (but not including) the leading edge of the epicardial echoes. C, Image at the mitral valve level, cursor line "2" in A. The motion of the anterior (AM) and posterior (PM) mitral leaflets is described by the letters shown. Diastolic opening of the valve occurs at point D and systolic closing occurs at point C (see text for more information). D, Image at the aortic root (Ao) level "3" (where valve cusps are seen). Diameter is measured at end diastole from the leading (anterior) edge of the anterior aortic wall to the leading edge of the posterior wall. The left atrium (LA; usually the auricular region) is measured at the time of peak anterior aortic movement. RV, Right ventricular lumen; RVW, right ventricular wall.

Measurements may also be taken from 2-D images if they are of high resolution and frames from the appropriate times in the cardiac cycle are used. Somatotype, breed, and body size greatly influence echo measurements in dogs. Endurance training also affects measured parameters, reflecting the increased cardiac mass and volume associated with frequent and sustained strenuous exercise. Some guidelines for approximate normal canine values are found in Table 2-3. Normal measurements in cats are more uniform but are also influenced by body size (Table 2-4). Chamber volume and ejection fraction are better estimated from optimized 2-D frames using the modified Simpsons' method rather than M-mode images because of greater potential for inaccurate geometric assumptions from one dimensional measurements (see Supplemental Readings for further information). The right parasternal long axis view is usually better for assessing LV size than the left apical view.

Diastolic measurements are made at the onset of the QRS complex of a simultaneously recorded ECG. Systolic measurements of the LV are made from the point of peak downward motion of the septum to the leading edge of the LV free-wall endocardium at the same instant. The septum and LV wall normally move toward each other in systole, although their peak movement may not coincide if electrical activation is not simultaneous. Paradoxic septal motion, in which the septum seems to move away from the LV wall and toward the transducer in systole, occurs in some cases of RV volume and/or pressure overload. This abnormal septal motion can also be visualized on 2-D images; it precludes accurate assessment of LV function using fractional shortening.

The fractional shortening (FS; % delta D) is commonly used to estimate LV function. FS is the percent change in LV dimension from diastole to systole ([LVIDd – LVIDs]/LVIDd × 100). Most normal dogs have an FS between 25% to 27% and 40%; in most cats FS is 35% to 65%, although there is some variability. It is important to note that this index, like others taken during cardiac ejection, has the significant limitation of being dependent on ventricular loading conditions. For example, reduced LV afterload (as occurs from mitral insufficiency, ventricular septal defect, or peripheral vasodilation) facilitates ejection of blood and permits greater

FS, although intrinsic myocardial contractility is not increased. The exaggerated FS in patients with severe mitral regurgitation causes the appearance of increased contractility in those with normal myocardial function and can mask deteriorating contractile function. Regional wall motion abnormalities as well as arrhythmias can affect the FS.

The use of the calculated end-systolic volume index (ESVI) has been suggested as a more accurate way to assess myocardial contractility in the presence of mitral regurgitation. This index (ESV/m² body surface area) compares ventricular size after ejection with body size rather than with the volume-overloaded end-diastolic ventricular size. LV volume estimation from 2-D rather than M-mode images is recommended. Extrapolation from human studies suggests an ESVI <30 ml/m² is normal, 30 to 60 ml/m² indicates mild LV systolic dysfunction, 60 to 90 ml/m² represents moderate LV dysfunction, and >90 ml/m² indicates severe LV dysfunction. A number of other methods can also be used to assess LV function.

Mitral valve motion is also evaluated with M-mode. The anterior (septal) leaflet is most prominent and has an "M" configuration. The posterior (parietal) leaflet is smaller; its motion mirrors the anterior leaflet, appearing as a "W." Tricuspid valve motion is similar. The mitral valve motion pattern is identified by letters (see Figure 2-26). Point E occurs at maximal opening of the valve during the rapid ventricular filling phase. The valve drifts into a more closed position (point F) at the end of rapid ventricular filling. Atrial contraction causes the valve to open again (point A). At rapid heart rates the E and A points can merge. The mitral valve closes (point C) at the onset of ventricular systole. In normal animals the mitral E point is close to the interventricular septum. Increased E point-to-septal separation is usually associated with reduced myocardial contractility, but aortic insufficiency can also cause this. In animals with IV outflow obstruction, hemodynamic forces during ejection can pull the anterior mitral leaflet toward the septum. This is called systolic anterior motion (SAM), and it causes the normally straight mitral echos (between points C and D) to bend toward the septum during systole (see Figure 8-4). Diastolic flutter of the anterior mitral leaflet can sometimes



TABLE 2-4

Echocardiographic Measurement Guidelines for Cats\*

LVID <sub>D</sub> (mm)	LVID <sub>s</sub> (mm)	LVID <sub>s</sub> (mm) LVW <sub>p</sub> (mm)		LVW <sub>s</sub> (mm) IVS <sub>D</sub> (mm)		LA† (mm)	AO (mm)
12-18	5-10	≤5.5	≤9	≤5.5	≤9	7-14	8-11

FS 35%-65%

EPSS ≤4 mm

LVID<sub>d</sub>, Left ventricular internal diameter at end diastale; LVID<sub>s</sub>, left ventricular internal diameter at end systole; LVW<sub>d</sub>, left ventricular wall at end diastale; LVW<sub>s</sub>, left ventricular wall at end systole; IVS<sub>d</sub>, interventricular septum at end systole; LA, left atrium (systole); Ao, aortic root; FS, fractional shortening; EPSS, mitral E-point septal separation.

<sup>\*</sup>These values are based on the author's experience and compilation of published studies. Ketamine increases heart rate and decreases LVID<sub>d</sub>. See Suggested Readings for additional references.

<sup>†</sup>Orientation of M-mode cursor across the LA is variable among animals; maximal LA dimension is best assessed by 2-D imaging.

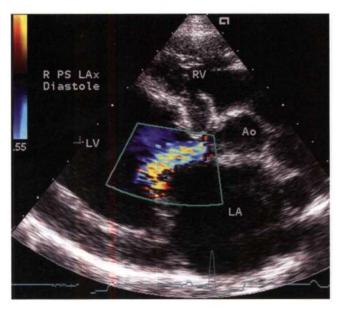


FIG 2-27

Color flow Doppler image of an aortic regurgitation jet angled toward and along the anterior leaflet of the mitral valve in a 2-year-old Rottweiler with aortic valve endocarditis. The regurgitant jet causes the mitral leaflet to flutter in diastole as seen in Fig. 2-28. Imaged from the right parasternal long axis position. Ao, Aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

be seen when an aortic insufficiency jet causes the leaflet to vibrate (Figures 2-27 and 2-28).

The diameter of the aortic root and sometimes its motion are measured with M-mode. The parallel walls of the aortic root shift rightward in systole. During diastole one or two aortic valve cusps may be seen as a straight line parallel to and centered between the aortic wall echoes. At the onset of ejection, the cusps separate toward the walls of the aortic root and then come together again at the end of ejection. The shape of these echoes (two cusps) has been described as a train of boxcars or little rectangular boxes attached together by a string. Aortic diameter is measured at end diastole. The amplitude of posterior-to-anterior motion of the aortic root is often decreased in animals with poor cardiac output. The LA dimension (behind the aortic root) is measured at maximal systolic excursion. In normal cats and dogs, the (M-mode) ratio of LA to aortic root diameters is about 1 to 1. However, LA size is underestimated with this M-mode view because (especially in dogs) the M-mode cursor usually transects the LA close to the left auricle, not at its maximal dimension. In cats the M-mode beam is more likely to cross the body of the LA, but its orientation can be inconsistent. Echo beam placement may be difficult in some animals, and the pulmonary artery can be inadvertently imaged instead. Therefore LA size assessment is best done from 2-D images.

Systolic time intervals (STIs) have been used sporadically to estimate cardiac function, but they are influenced by cardiac filling and afterload. These intervals can be calculated if the opening and closing of the aortic valve are clearly seen on M-mode and a simultaneous ECG is recorded for timing. The STIs are left ventricular ejection time (duration of time the aortic valve is open), preejection period (time from the onset of the QRS to aortic valve opening), and total electromechanical systole (left ventricular ejection time plus preejection period). STIs can also be derived with Doppler echocardiography.

# **CONTRAST ECHOCARDIOGRAPHY**

This technique, often called a "bubble study," uses rapid injection of a substance containing "microbubbles" either into a peripheral vein or selectively into the heart. These microbubbles generate tiny pinpoint echos that temporarily opacify the blood pool being imaged (Fig. 2-29). The microbubbles appear as bright sparkles moving with the blood flow. Agitated saline solution, a mixture of saline and the patient's blood, and other substances can be used as echocontrast material. Injection into a peripheral vein opacifies the right heart chambers; bubbles seen in the left heart or aorta indicate a right-to-left shunt. Saline microbubbles do not pass through the pulmonary capillaries (although some commercially available echo-contrast agents do), so echocontrast injection via selective left-sided heart catheterization is required to visualize intracardiac left-to-right shunts or mitral regurgitation. Doppler echocardiography has largely replaced echocontrast studies, but they are still a useful tool in some cases.

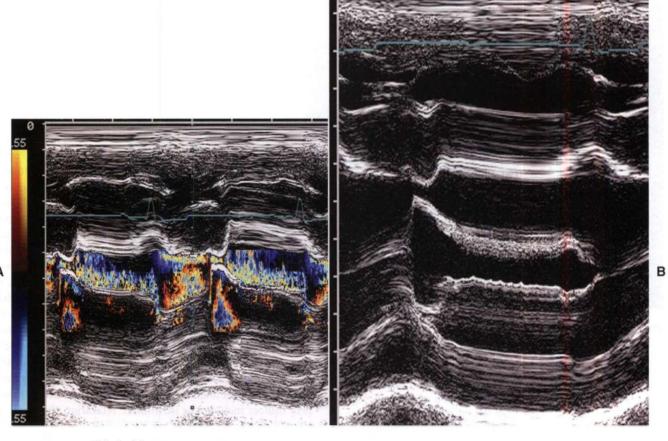
# DOPPLER ECHOCARDIOGRAPHY

Blood flow direction and velocity are imaged with Doppler echocardiography. Several types of Doppler echocardiography are used clinically: pulsed-wave (PW), continuous-wave (CW), and color flow (CF) mapping. Important clinical applications relate to identifying abnormal flow direction or turbulence and increased flow velocity. This allows detection and quantification of valvular insufficiency, obstructive lesions, and cardiac shunts. Cardiac output and other indicators of systolic function can be assessed, and there is much interest in Doppler-derived indices of diastolic function in patients with cardiac disease (see Suggested Readings). Adequate Doppler examinations are technically demanding. They are often very time consuming and require a good understanding of hemodynamic principles and cardiac anatomy.

The Doppler modality is based on detecting frequency shifts between the emitted ultrasound energy and echoes reflected from moving blood cells (the Doppler shift\*). Echoes returning from cells moving away from the transducer are of lower frequency, and those from cells moving toward the transducer are of higher frequency. The higher

<sup>\*</sup> $V = C(\pm \Delta f/2f_0\cos\theta)$ 

V, calculated blood flow velocity (meters/sec); C, speed of sound in soft tissue (1540 meters/sec);  $\pm$   $\Delta f$ , Doppler frequency shift;  $f_0$ , transmitted frequency;  $\theta$ , intercept angle (between ultrasound beam and blood flow direction).



Color M-mode (A) and standard M-mode (B) images of the mitral valve from the dog in Fig. 2-27. The disturbed flow from aortic regurgitation is seen as the colors along the anterior leaflet in the left ventricular outflow region. Fine fluttering of the anterior mitral leaflet is seen in B; the leaflet appears wide and "fuzzy" compared with the thin, discrete posterior leaflet.

the velocity of the cells, the greater the frequency shift. Optimal blood flow profiles and calculation of maximal blood flow velocity are possible when the ultrasound beam is aligned parallel to the flow. This is in contrast to the perpendicular beam orientation needed for optimal M-mode and 2-D imaging. With Doppler, calculated blood flow velocity diminishes as the angle of incidence between ultrasound beam and direction of blood flow diverges from 0 degrees. This is because the calculated flow velocity is inversely related to the cosine of this angle (cosine 0 degrees = 1). As long as the angle between the ultrasound beam and path of blood flow is less than 20 degrees, maximal flow velocity can be estimated with reasonable accuracy. As this angle of incidence increases, the calculated velocity decreases. At an angle of 90 degrees, the calculated velocity is 0 (cosine 90 degrees = 0); therefore no flow signal is recorded when the ultrasound beam is perpendicular to blood flow. Flow signals are usually displayed with time on the x axis and velocity (scaled in m/sec) on the y axis. A zero baseline demarcates flow away from (below baseline) or toward (above baseline) the transducer. Higher velocities are displayed farther from baseline. Other flow characteristics (e.g., turbulence) also affect the Doppler spectral display.

# **Pulsed Wave Doppler**

Pulsed wave (PW) Doppler uses short bursts of ultrasound to analyze echoes returned from a specified area (designated the sample volume) along the Doppler cursor line. The advantage of PW Doppler is that blood flow velocity, direction, and spectral characteristics can be calculated from a specific location in the heart or blood vessel. The main disadvantage is that the maximum measurable velocity is limited. The pulse repetition frequency (time required to send, receive, and process returning echoes), as well as the transmitted frequency and the distance of the sample volume from the transducer determine the maximum measurable velocity (called the *Nyquist limit*). The Nyquist limit is defined by two times the pulse repetition frequency. Lower frequency transducers and closer sample volume placement increase the Nyquist limit. When blood flow velocity is



FIG 2-29

Echo "bubble" study in a dog with pulmonary hypertension. Bright speckles fill the RA and RV chambers after an injection of agitated saline into a peripheral vein. Because there was no intracardiac shunt in this dog, no "bubbles" are seen in the left heart chambers, despite abnormally high right heart pressures. View from left apical position; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

higher than the Nyquist limit, "aliasing" or velocity ambiguity occurs. This is displayed as a band of velocity signals extending above and below ("wrapped around") the baseline, so neither velocity nor direction is measurable (Fig. 2-30). The velocity spectrum displayed with PW Doppler when blood cells in the sample volume are moving in the same direction and at the same velocity is relatively thin (tight). Variation in velocity causes spectral broadening (widening).

Characteristic blood flow patterns are obtained from the different valve areas. Flow across both AV valves has a similar pattern; likewise, flow patterns across the semilunar valve areas are similar. Normal diastolic flow across the mitral valve (Fig. 2-31) and tricuspid valve consists of an initial higher velocity signal during the rapid ventricular filling phase (E wave), which is followed by a smaller velocity signal associated with atrial contraction (A wave). Breed, age, and body weight appear to have little influence on normal Doppler measurements. Peak velocities are normally higher across the mitral (peak E usually 0.9 to 1.0 m/sec; peak A usually 0.6 to 0.7 m/sec) compared with the tricuspid valve (peak E usually 0.8 to 0.9 m/sec; peak A usually 0.5 to 0.6 m/sec). The four-chamber left apical view usually provides optimal alignment for assessing mitral inflow velocities; the left cranial short axis view is usually best for tricuspid inflow, although several other imaging planes may provide adequate alignment. Doppler-derived diastolic function indices include the isovolumic relaxation time, mitral valve E/A ratio, and others.

Flow across the pulmonary and aortic valves (Fig. 2-32) accelerates rapidly during ejection, with more gradual decel-

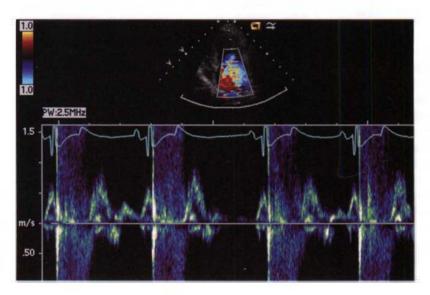


FIG 2-30

Mitral diastolic inflow and systolic regurgitant flow in a dog with degenerative mitral valve disease recorded with PW Doppler from left caudal parasternal position. The direction of mitral regurgitant flow is away from the transducer (below baseline); however, this direction cannot be discerned with PW because the flow velocity is too high. The signal is instead "wrapped around" the baseline (aliased).



FIG 2-31

Normal mitral valve inflow recorded with PW Doppler from left caudal parasternal position in a dog. The flow signal (above baseline) following the QRS-T of the ECG represents early diastolic flow into the ventricle (E); the second, smaller peak after the P wave represents inflow from atrial contraction (A). Velocity scale in meters/second is on the left.

eration. Peak systolic pulmonary velocity is 1.4 to 1.5 m/sec in most normal dogs. The left cranial views usually provide better flow alignment. Sample volume placement is at or just distal to the valve. Peak aortic velocity is usually <1.6 to 1.7 m/sec, although some normal dogs have peak aortic velocities above 2 m/sec related to increased stroke volume or high sympathetic tone, especially if unsedated. Ventricular outflow obstruction causes more rapid flow acceleration, increased peak velocity, and turbulence. In general, aortic velocities over 2.2 (-2.4) m/sec are suggestive of outflow obstruction. Between 1.7 and ~2.2 m/sec lies a "grey zone" where mild LV outflow obstruction (e.g., some cases of subaortic stenosis) cannot be differentiated with certainty from normal but vigorous left ventricular ejection. Maximal aortic/LV outflow velocities are obtained in most dogs from the subcostal (subxiphoid) position; however, in some dogs the left apical view provides higher velocity recordings. The LV outflow region should be interrogated from both views and the greater maximal velocity value used.

# **Continuous Wave Doppler**

Continuous wave (CW) Doppler employs continuous and simultaneous ultrasound transmission and reception along the line of interrogation. Theoretically, there is no maximum velocity limit with CW Doppler, so high-velocity flows can be measured (Fig. 2-33). The disadvantage of CW Doppler is that sampling of blood flow velocity and direction occurs all along the ultrasound beam, not in a specified area (so-called range ambiguity).

# **Pressure Gradient Estimation**

Doppler estimation of pressure gradients is used in combination with M-mode and 2-D imaging to assess the severity of congenital or acquired flow obstructions. In addition, regurgitant jet maximal velocity estimates the peak pressure gradient across the regurgitant valve. The instantaneous pressure gradient across a stenotic or regurgitant valve is estimated using the maximal measured velocity of the flow jet. CF Doppler is useful to depict jet orientation. Careful Doppler beam alignment is essential in order to measure maximum velocity. CW Doppler is employed if aliasing occurs with PW Doppler. A modification of the Bernoulli equation is used to estimate pressure gradient:

# Pressure gradient = $4(\text{maximum velocity})^2$

Other factors involved in this relationship are usually of minimal clinical importance and are generally ignored.

Pulmonary arterial systolic pressure can be estimated (if there is no pulmonic stenosis) by using the maximal tricuspid regurgitation jet velocity (TRmax). The calculated systolic pressure gradient plus about 8 to 10 mm Hg (or the measured central venous pressure) equals the peak right ventricular systolic pressure, which approximates pulmonary artery systolic pressure. Pulmonary hypertension (PH) is associated when TRmax exceeds 2.8 m/s. The severity of PH is often categorized as mild (~35-50 mm Hg; TRmax 2.9-3.5 m/s), moderate (~51-75 mm Hg; TRmax 3.6-4.3 m/s), or severe (>75 mm Hg; TRmax >4.3 m/s). Likewise, pulmonary diastolic pressure can be estimated from pulmonary



Normal pulmonary flow recorded with PW Doppler from left cranial short-axis position in a dog. There is rapid blood acceleration (below baseline) into the pulmonary artery, with a peak velocity of about 1.0 m/sec. Velocity scale in meters per second is on the left.

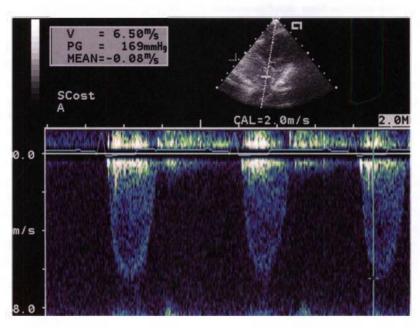
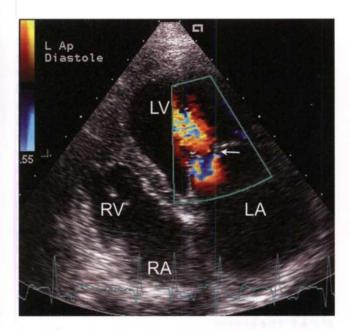


FIG 2-33
CW Doppler recording of high-velocity aortic outflow in a dog with severe subaortic stenosis, imaged from the subcostal position. Estimated systolic pressure gradient across the outflow region is 169 mm Hg based on a peak velocity of 6.5 m/sec. Velocity scale in meters/second is on the left.

regurgitant (PR) jet velocity at end-diastole. The calculated end-diastolic pressure gradient between the pulmonary artery and the right ventricle, plus the estimated right ventricular diastolic pressure, represents pulmonary arterial diastolic pressure. Pulmonary hypertension is also suggested by a peak PR velocity of >2.2 m/s.

## **Color Flow Mapping**

Color flow (CF) mapping is a form of PW Doppler that combines the M-mode or 2-D modality with blood flow imaging. However, instead of one sample volume along one scan line, many sample volumes are analyzed along multiple scan lines. The mean frequency shifts obtained



Nyquist limit, causing red-coded flow (blood moving toward transducer) to alias to blue, then again to red, and once more to blue. Turbulent flow is seen within the left ventricle at the top of the 2-D image.

from multiple sample volumes are color-coded for direction (in relation to the transducer) and velocity. Most systems code blood flow toward the transducer as red and blood flow away from the transducer as blue. Zero velocity is indicated by black, meaning either no flow or flow that is perpendicular to the angle of incidence. Differences in relative velocity of flow can be accentuated, and the presence of multiple velocities and directions of flow (turbulence) can be indicated by different display maps that use variations in brightness and color. Aliasing occurs often, even with normal blood flows, because of low Nyquist limits. Signal aliasing is displayed as a reversal of color (e.g., red shifting to blue; Fig. 2-34). Turbulence produces multiple velocities and directions of flow in an area, resulting in a mixing of color; this display can be enhanced using a variance map, which adds shades of yellow or green to the red/blue display (Fig. 2-35).

The severity of valve regurgitation is sometimes estimated by the size and shape of the regurgitant jet during CF imaging. Although technical and hemodynamic factors confound the accuracy of such assessment, wide and long regurgitant jets are generally associated with more severe regurgitation than narrow jets. Other methods for quantifying valve regurgitation have been described as well. Maximum regurgitant jet velocity is not a good indicator of severity, especially with mitral regurgitation. Changes in chamber size provide a better indication of severity with chronic regurgitation.

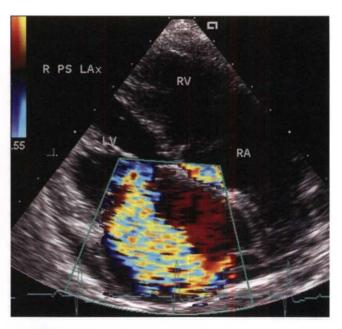


FIG 2-35
Systolic frame showing turbulent regurgitant flow into the enlarged LA of a dog with chronic mitral valve disease. The regurgitant jet curves around the dorsal aspect of the LA. Imaged from the right parasternal long axis, four chamber view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

## **Doppler Tissue Imaging**

Doppler tissue imaging (DTI) is a modality used to assess the motion of tissue, rather than blood cells, by altering the signal processing and filtering of returning echoes. Myocardial velocity patterns can be assessed with color flow and pulsed wave spectral DTI techniques. Spectral DTI provides greater temporal resolution and quantifies velocity of myocardial motion at specific locations, such as the lateral or septal aspects of the mitral annulus (Fig. 2-36). Color DTI methods display mean myocardial velocities from different regions. Other techniques used to assess regional myocardial function and synchrony are derived from DTI methods; these include myocardial velocity gradients, myocardial strain, strain rate, and velocity vector imaging.

# TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) uses specialized transducers mounted on a flexible, steerable endoscope tip to image cardiac structures through the esophageal wall. TEE can provide clearer images of some cardiac structures (especially those at or above the AV junction) compared with transthoracic echocardiography because chest wall and lung interference is avoided. This technique can be particularly useful for defining some congenital cardiac defects and identifying thrombi, tumors, or endocarditis lesions, as well as guiding cardiac interventional procedures (Fig. 2-37). The need for general anesthesia and the expense of the

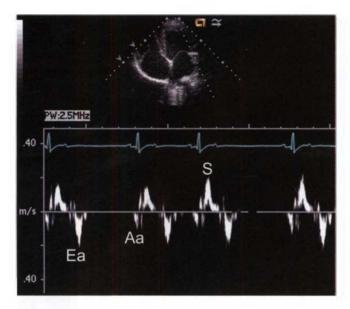


FIG 2-36

PW Doppler tissue image from a cat. The mitral annulus moves toward the left apex (and transducer) in systole (S). Early diastolic filling (Ea) shifts the annulus away from the apex as the LV expands. Additional motion occurs with late diastolic filling from atrial contraction (Aa).

endoscopic transducers are the main disadvantages of TEE. Complications related to the endoscopy procedure appear to be minimal.

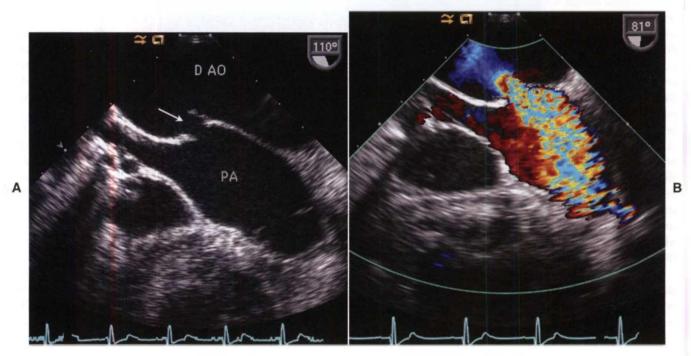
## THREE-DIMENSIONAL **ECHOCARDIOGRAPHY**

The ability to generate and manipulate 3-dimensional (3-D) images of the heart and other structures is a promising new way to evaluate cardiac structure and function. Anatomic and blood flow abnormalities can be viewed from any angle by rotating or bisecting the 3-D images. Current technology requires several cardiac cycles in order to acquire sufficient data for 3-D reconstruction of the entire heart, although true "real time" 3-D echocardiography will soon be available.

## OTHER TECHNIQUES

## **CENTRAL VENOUS PRESSURE MEASUREMENT**

Central venous pressure (CVP) is influenced by intravascular volume, venous compliance, and cardiac function. CVP measurement helps in differentiating high right heart filling pressure (as from right heart failure or pericardial disease) from other causes of pleural or peritoneal effusion. But it is important to note that pleural effusion itself can increase intrapleural pressure enough to impair cardiac filling; this



A, Two-dimensional transesophageal echo (TEE) image at the heartbase from a 5-year-old English Springer Spaniel shows a patent ductus arteriosus (arrow) between the descending aorta (D Ao) and pulmonary artery (PA). B, Color flow Doppler image in diastole from the same orientation demonstrates flow acceleration toward the ductal opening in the D Ao and the turbulent ductal flow into the PA.

can raise CVP even in the absence of cardiac discase. Therefore CVP should be measured after thoracocentesis in patients with moderate- to large-volume pleural effusion. CVP is sometimes used to monitor critical patients receiving large intravenous fluid infusions. However, CVP is not an accurate reflection of left heart filling pressure and thus is not a reliable way to monitor for cardiogenic pulmonary edema. The CVP in normal dogs and cats usually ranges from 0 to 8 (up to 10) cm H<sub>2</sub>O. Fluctuations in CVP that parallel those of intrapleural pressure occur during respiration.

CVP is measured via a large-bore jugular catheter that extends into or close to the right atrium. The catheter is placed aseptically and connected by extension tubing and a three-way stopcock to a fluid administration set. A water manometer is attached to the stopcock and positioned vertically, with the stopcock (representing 0 cm H2O) placed at the same horizontal level as the patient's right atrium. The stopcock is turned off to the animal, allowing the manometer to fill with crystalloid fluid; then the stopcock is turned off to the fluid reservoir so that the fluid column in the manometer equilibrates with the animal's CVP. Repeated measurements are more consistent when taken with the animal and manometer in the same position and during the expiratory phase of respiration. Small fluctuations in the manometer's fluid meniscus occur with the heartbeat, and slightly larger movement is associated with respiration. Marked change in the height of the fluid column associated with the heartbeat suggests either severe tricuspid insufficiency or that the catheter tip is within the right ventricle.

## **BIOCHEMICAL MARKERS**

A number of specific biochemical markers are being evaluated for their diagnostic and prognostic potential. Cardiac troponins are more sensitive for detecting myocardial injury than cardiac-specific creatine kinase (CK-MB) and other biochemical markers of muscle damage. In dogs the CK-MB isoform comprises only a minority of total cardiac CK, and it is also present in noncardiac tissues. Cardiac troponins are regulatory proteins associated with cardiac actin (thin) contractile filaments. Circulating concentrations of cardiac troponin I (cTnI) and cardiac troponin T (cTnT) provide a specific indicator of myocardial injury or necrosis. The pattern and degree of their release can depend on the type and severity of myocyte injury. Although there is an association between acute injury and the degree of increase in serum troponin concentration, this relationship is less clear in patients with chronic disease. After acute myocyte damage, serum cTn concentration increases within a few hours, peaks in 12 to 24 hours, and then declines over the next few weeks. Myocardial inflammation, trauma, congestive heart failure, hypertrophic cardiomyopathy, and gastric dilatation/volvulus have been associated with increased cardiac toponin concentrations. In dogs with congestive heart failure or hypertrophic cardiomyopathy, this probably relates to continued myocardial remodeling, not just acute damage from myocardial infarction. cTnI appears to be more specific than cTnT. Human assays for cTnI and cTnT can be used in dogs and cats, but because methodology is not standardized among various cTnI assays, the cut-off values for normal may vary. Furthermore, cTn values that indicate clinically relevant myocardial disease or damage in animals are unclear.

The natriuretic peptides, ANP, BNP, and their precursors, are other potentially useful biomarkers for assessing the presence and possibly prognosis of heart failure. Circulating natriuretic peptide concentrations increase in association with vascular volume expansion and decreased renal clearance and when their production is stimulated (e.g., with ventricular strain and hypertrophy, hypoxia, or tachycardia). The natriuretic peptides should be used as functional markers of cardiac disease rather than of specific pathology. Issues of standardization among different commercial assays and methodologies and lack of universal reference values are limitations. The N-terminal fragments (NT-proANP and NT-proBNP) of the natriuretic peptide precursor molecules remain in circulation longer and reach higher plasma concentrations than the active hormone molecules. Because ANP and NT-proANP amino acid sequences are highly conserved among people, dogs, and cats, human assays may be used. Canine and feline BNP are similar, but differences from people preclude the use of most human BNP assays. Canine and feline NT-proBNP measurement is commercially available, although questions regarding interpretation of results remain. Plasma BNP and NT-proBNP are sensitive and specific markers for chronic LV dysfunction in people, and high concentrations are negatively correlated with prognosis. BNP as well as NT-proANP are high in most cats with hypertrophic cardiomyopathy. Elevated concentrations are also seen in dogs with heart disease and heart failure, but overlap in these concentrations compared with those of some dogs without heart disease is of concern. Studies are ongoing to clarify the potential usefulness of plasma natriuretic peptides in dogs with cardiac disease.

Other biomarkers are currently being evaluated. The endothelin (ET) system is activated in dogs and cats with heart failure and in those with pulmonary hypertension, so assays for plasma ET-like immunoreactivity may be useful. Tumor necrosis factor (TNF $_{\alpha}$ ) may also be a useful marker of cardiac disease progression, but it is not cardiac specific.

### **ANGIOCARDIOGRAPHY**

Nonselective angiocardiography can be used to diagnose several acquired and congenital diseases, including cardiomyopathy and heartworm disease in cats, severe pulmonic or (sub)aortic stenosis, patent ductus arteriosus, and tetralogy of Fallot. Intracardiac septal defects and valvular regurgitation cannot be reliably identified. The quality of such studies is higher with rapid injection of radiopaque agents via a large-bore catheter and with smaller patient size. In most cases, echocardiography provides similar information more safely. However, evaluation of the pulmonary vasculature is better accomplished using nonselective angiocardiography.

Selective angiocardiography is performed by advancing cardiac catheters into specific areas of the heart or great vessels. Injection of contrast material is generally preceded by the measurement of pressures and oxygen saturations. This technique allows identification of anatomic abnormalities and the path of blood flow. Doppler echocardiography may provide comparable diagnostic information noninvasively. However, selective angiography is a necessary component of many cardiac interventional procedures.

## CARDIAC CATHETERIZATION

Cardiac catheterization allows measurement of pressure, cardiac output, and blood oxygen concentration from specific intracardiac locations. Specialized catheters are selectively placed into different areas of the heart and vasculature via the jugular vein, carotid artery, or the femoral vessels. Congenital and acquired cardiac abnormalities can be identified and assessed with these procedures in combination with selective angiocardiography. The advantages of Doppler echocardiography often outweigh those of cardiac catheterization, especially in view of the good correlation between certain Doppler- and catheterization-derived measurements. However, cardiac catheterization is necessary for balloon valvuloplasty, ductal occlusion, and other interventional procedures.

Pulmonary capillary wedge pressure (PCWP) monitoring is sometimes performed in dogs with heart failure because it provides an estimate of left heart filling pressure (in the absence of left ventricular inflow obstruction). To obtain PCWP, an end-hole, balloon-tipped (Swan-Ganz) catheter is passed into the main pulmonary artery. When the balloon is inflated and the catheter allowed to become wedged in a smaller pulmonary artery, flow in that vessel is occluded. The pressure measured at the catheter tip reflects pulmonary capillary pressure, which essentially is equivalent to left atrial pressure. This invasive technique allows differentiation of cardiogenic from noncardiogenic pulmonary edema and provides a means of monitoring the effectiveness of heart failure therapy. However, its use requires meticulous, aseptic catheter placement and continuous patient monitoring.

# OTHER NONINVASIVE IMAGING Nuclear Cardiology

Radionuclide, or nuclear, methods of evaluating cardiac function are available at some veterinary referral centers. These techniques can provide noninvasive assessment of cardiac output, ejection fraction, and other measures of cardiac performance as well as myocardial blood flow and metabolism.

## Cardiac Computed Tomography and Magnetic Resonance Imaging

Cardiac computed tomography and magnetic resonance imaging are available in some centers. These techniques depict greater contrast between cardiovascular structures and the blood pool as well as differentiate certain types of tissue. Because cardiac movement during the imaging sequence reduces image quality, some type of physiologic (ECG) gating, as well as rapid image acquisition, are needed. Identification of pathologic morphology is a major application, although myocardial function, perfusion, and blood flow studies may be done depending on the technical capability of the equipment. Novel MR techniques also allow noninvasive evaluation of blood vessels, including calculation of peripheral resistance.

#### **PNEUMOPERICARDIOGRAPHY**

Pneumopericardiography may be helpful in delineating the cause of pericardial effusions, especially if echocardiography is unavailable. This technique and pericardiocentesis are described in Chapter 9.

### **ENDOMYOCARDIAL BIOPSY**

Small samples of endocardium and adjacent myocardium can be obtained using a special bioptome passed into the right ventricle via a jugular vein. Routine histopathology and other techniques to evaluate myocardial metabolic abnormalities can be performed on the biopsy samples. Endomyocardial biopsy is most often used for myocardial disease research and is not commonly used in clinical veterinary cardiology.

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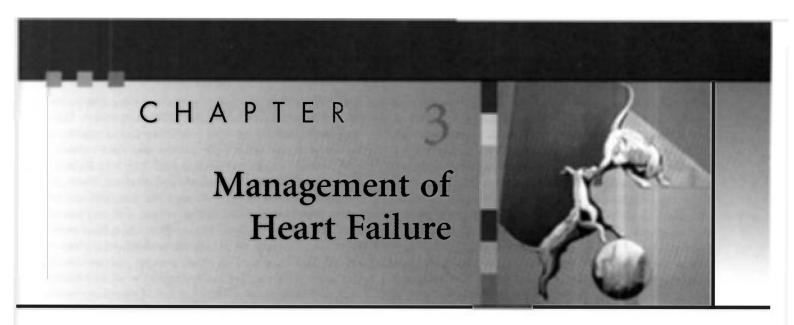
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## CHAPTER OUTLINE

#### **OVERVIEW OF HEART FAILURE**

Cardiac Responses Systemic Responses

General Causes of Heart Failure

Approach to Treating Heart Failure

## reatment for acute congestive

**HEART FAILURE** 

General Considerations

Supplemental Oxygen

Drug Therapy

Heart Failure Caused by Diastolic Dysfunction

Monitoring and Follow-Up

#### MANAGEMENT OF CHRONIC HEART FAILURE

General Considerations

**Diuretics** 

Angiotensin Converting Enzyme Inhibitors

Positive Inotropic Agents

Other Vasodilators

**Dietary Considerations** 

Chronic Diastolic Dysfunction

Reevaluation and Monitoring

Strategies for Refractory Congestive Heart Failure

## OVERVIEW OF HEART FAILURE

Heart failure entails abnormalities of cardiac systolic or diastolic function, or both. These can occur without evidence of abnormal fluid accumulation (congestion), especially in the initial stages of disease. Congestive heart failure (CHF) is characterized by high cardiac filling pressure, which leads to venous congestion and tissue fluid accumulation. It is a complex clinical syndrome rather than a specific etiologic diagnosis. The pathophysiology of heart failure is complex. It involves structural and functional changes within the heart and vasculature as well as other organs. The process of progressive cardiac remodeling inherent to heart failure can develop secondary to cardiac injury or stress from valvular

disease, genetic mutations, acute inflammation, ischemia, increased systolic pressure load, and other causes.

#### CARDIAC RESPONSES

Cardiac remodeling refers to the changes in myocardial size, shape, and stiffness that occur in response to various mechanical, biochemical, and molecular signals induced by the underlying injury or stress. These changes include myocardial cell hypertrophy, cardiac cell drop-out or selfdestruction (apoptosis), excessive interstitial matrix formation, fibrosis, and destruction of normal collagen binding between individual myocytes. The latter, resulting from effects of myocardial collagenases or matrix metalloproteinases, can cause dilation or distortion of the ventricle from myocyte slippage. Stimuli for remodeling include mechanical forces (e.g., increased wall stress from volume or pressure overload) and also various neurohormones (e.g., angiotensin II, norepinephrine, endothelin, aldosterone) and cytokines (e.g., tumor necrosis factor [TNF]-alpha). Contributing biochemical abnormalities related to cellular energy production, calcium fluxes, protein synthesis, and catecholamine metabolism have been variably identified in different models of heart failure and in clinical patients. Myocyte hypertrophy and reactive fibrosis increase total cardiac mass by eccentric and, in some cases, concentric patterns of hypertrophy. Ventricular hypertrophy can increase chamber stiffness, impair relaxation, and increase filling pressures; these abnormalities of diastolic function can also contribute to systolic failure. Ventricular remodeling also promotes the development of arrhythmias. The initiating stimulus underlying chronic cardiac remodeling may occur years before clinical evidence of heart failure appears.

Acute increases in ventricular filling (preload) induce greater contraction force and blood ejection. This response, known as the Frank-Starling mechanism, allows beat-to-beat adjustments that balance the output of the two ventricles and increase overall cardiac output in response to acute increases in hemodynamic load. The Frank-Starling effect helps normalize cardiac output under conditions of increased pressure and/or volume loading, but these conditions also increase ventricular wall stress and oxygen consumption.

Ventricular wall stress is directly related to ventricular pressure and internal dimensions and inversely related to wall thickness (Laplace's law). Myocardial hypertrophy can reduce wall stress. The pattern of hypertrophy that develops depends on the underlying disease. A ventricular systolic pressure load induces "concentric" hypertrophy; myocardial fibers and ventricular walls thicken as contractile units are added in parallel. A volume load causes "eccentric" hypertrophy; myocardial fiber elongation and chamber dilation occur as new sarcomeres are laid down in series. Compensatory hypertrophy lessens the importance of the Frank-Starling mechanism in stable, chronic heart failure. Although volume loads are better tolerated because myocardial oxygen demand is not as severe, both abnormal pressure and volume loading impair cardiac performance over time. Eventually, decompensation and myocardial failure develop. In patients with primary myocardial diseases, initial cardiac pressure and volume loads are normal, but intrinsic defects of the heart muscle lead to the hypertrophy and dilation observed.

Cardiac hypertrophy and other remodeling begin long before heart failure becomes manifest. In addition to myocyte hypertrophy, cardiac remodeling can include cell loss or self-destruction (apoptosis), excessive interstitial matrix formation, and loss of normal collagen binding. Myocyte hypertrophy and reactive fibrosis increase total cardiac mass as well as ventricular stiffness. This promotes elevated filling pressures and predisposes the patient to ischemia. Increased chamber size increases wall stress and myocardial O<sub>2</sub> demand. Biochemical abnormalities involving cell energy production, calcium fluxes, and contractile protein function can develop. Clinical heart failure can be considered a state of decompensated hypertrophy; ventricular function progressively deteriorates as contractility and relaxation become more deranged.

Continued exposure to increased sympathetic stimulation reduces cardiac sensitivity to catecholamines. Downregulation (reduced number) of myocardial  $\beta_1$ -receptors and other changes in cellular signaling may help protect the myocardium against the cardiotoxic and arrhythmogenic effects of catecholamines. Beta-blocking agents can reverse  $\beta_1$ -receptor down-regulation but may worsen heart failure. Cardiac  $\beta_2$ - and  $\alpha_1$ -receptors are also present but are not down-regulated; these are thought to contribute to myocardial remodeling and arrhythmogenesis. Another cardiac receptor subtype ( $\beta_3$ -receptors) may promote myocardial function deterioration through a negative inotropic effect.

# SYSTEMIC RESPONSES Neurohormonal Mechanisms

Neurohormonal (NH) responses contribute to cardiac remodeling and also have more far-reaching effects. Over time, excessive activation of neurohormonal "compensatory" mechanisms leads to the clinical syndrome of CHF. Although these mechanisms support circulation in the face of acute hypotension and hypovolemia, their chronic activation accelerates further deterioration of cardiac function. Major neurohormonal changes in heart failure include increases in sympathetic nervous tone, attenuated vagal tone,

activation of the renin-angiotensin-aldosterone system, and release of antidiuretic hormone (ADH-vasopressin). These neurohormonal systems work independently and together to increase vascular volume (by sodium and water retention and increased thirst) and vascular tone (Fig. 3-1). Excessive volume retention results in edema and effusions. Prolonged systemic vasoconstriction increases the workload on the heart, can reduce forward cardiac output, and may exacerbate valvular regurgitation. The extent to which these mechanisms are activated varies with the severity and etiology of heart failure. In general, as failure worsens, neurohormonal activation increases. Increased production of endothelins and proinflammatory cytokines, as well as altered expression of vasodilatory and natriuretic factors, also contribute to the complex interplay among these NH mechanisms and their consequences.

The effects of sympathetic stimulation (e.g., increased contractility, heart rate, and venous return) can increase cardiac output initially, but over time these effects become detrimental by increasing afterload stress and myocardial oxygen requirements, contributing to cellular damage and myocardial fibrosis, and enhancing the potential for cardiac arrhythmias. Normal feedback regulation of sympathetic nervous and hormonal systems depends on arterial and atrial baroreceptor function. Baroreceptor responsiveness becomes attenuated in chronic heart failure, which contributes to sustained sympathetic and hormonal activation and reduced inhibitory vagal effects. Baroreceptor function can improve with reversal of heart failure, increased myocardial contractility, decreased cardiac loading conditions, or inhibition of angiotensin II (which directly attenuates baroreceptor sensitivity). Digoxin has a positive effect on baroreceptor sensitivity.

The renin-angiotensin system has far-reaching effects. Whether systemic renin-angiotensin-aldosterone activation always occurs before overt congestive failure is unclear, and may depend on the underlying etiology. Renin release from the renal juxtaglomerular apparatus occurs secondary to low renal artery perfusion pressure, renal β-adrenergic receptor stimulation, and reduced Na+ delivery to the macula densa of the distal renal tubule. Stringent dietary salt restriction and diuretic or vasodilator therapy can promote renin release. Renin facilitates conversion of the precursor peptide angiotensinogen to angiotensin I (an inactive form). Angiotensin-converting enzyme (ACE), found in the lung and elsewhere, converts angiotensin I to the active angiotensin II and is involved in the degradation of certain vasodilator kinins. There are also other pathways that generate angiotensin II.

Angiotensin II has several important effects, including potent vasoconstriction and stimulation of aldosterone release from the adrenal cortex. Additional effects of angiotensin II include increased thirst and salt appetite, facilitation of neuronal norepinephrine synthesis and release, blockade of neuronal norepinephrine reuptake, stimulation of antidiuretic hormone (vasopressin) release, and increased adrenal epinephrine secretion. Inhibition of ACE can reduce

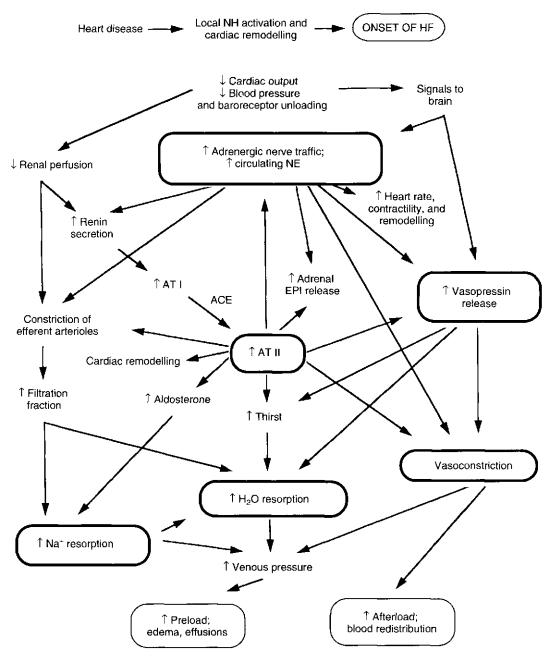


FIG 3-1
Major neurohormonal mechanisms leading to volume retention and increased afterload in congestive heart failure. ACE, Angiotensin-converting enzyme; AT, angiotensin; EPI, epinephrine; HF, heart failure; NE, norepinephrine.

NH activation and promote vasodilation and diuresis. Local production of angiotensin II also occurs in the heart, vasculature, adrenal glands, and other tissues. Local activity affects cardiovascular structure and function by enhancing sympathetic effects and promoting tissue remodeling that can include hypertrophy, inflammation, and fibrosis.

Aldosterone promotes sodium and chloride reabsorption as well as potassium and hydrogen ion secretion in the renal collecting tubules; the concurrent water reabsorption augments vascular volume. Increased aldosterone concentration can promote hypokalemia, hypomagnesemia, and impaired baroreceptor function. Aldosterone is also produced locally in the cardiovascular system and mediates inflammation and fibrosis. Chronic exposure can be detrimental to ventricular function and contribute to pathologic remodeling and myocardial fibrosis.

Antidiuretic hormone is released from the posterior pituitary gland. This hormone directly causes vasoconstriction and also promotes free water reabsorption in the distal nephrons. Although increased plasma osmolality or reduced blood volume are the normal stimuli for ADH release, reduced effective circulating volume and other nonosmotic stimuli

cause continued release of ADH in patients with heart failure. The continued release of ADH contributes to the dilutional hyponatremia sometimes found in patients with heart failure.

Increased circulating concentrations of other substances that play a role in abnormal myocardial hypertrophy and/or fibrosis, including cytokines (e.g.,  $TNF_{\alpha}$ ) and endothelins, have also been detected in animals with severe heart failure. Endothelin production is stimulated by hypoxia and vascular mechanical factors but also by angiotensin II, ADH, norepinephrine, cytokines (including  $TNF_{\alpha}$  and interleukin-I), and other factors.

Endogenous mechanisms that oppose the vasoconstrictor responses also are activated. These include natriuretic peptides, nitric oxide, and vasodilator prostaglandins. Normally, a balance between vasodilator and vasoconstrictor effects maintains circulatory homeostasis as well as renal solute excretion. As heart failure progresses, the influence of the vasoconstrictor mechanisms predominates despite increased activation of vasodilator mechanisms.

Natriuretic peptides are synthesized in the heart and play an important role in regulation of blood volume and pressure. Atrial natriuretic peptide (ANP) is synthesized by atrial myocytes as a prohormone, which is then cleaved to the active peptide after release stimulated by mechanical stretch of the atrial wall. Brain natriuretic peptide (BNP) is also synthesized in the heart, mainly by the ventricles in response to myocardial dysfunction or ischemia. Natriuretic peptides cause diuresis, natriuresis, and peripheral vasodilation. They act to antagonize the effects of the renin-angiotensin system and can also alter vascular permeability and inhibit growth of smooth muscle cells. Natriuretic peptides are degraded by neutral endopeptidases. Circulating concentrations of ANP and BNP increase in patients with heart failure. This increase has been correlated with pulmonary capillary wedge pressure and severity of heart failure in both dogs and people.

Nitric oxide (NO), produced in vascular endothelium in response to endothelial-nitric oxide synthetase (NOS), is a functional antagonist of endothelin and angiotensin II. This response is impaired in patients with heart failure. At the same time, myocardial inducible—NOS expression is enhanced; myocardial NO release has negative effects on myocyte function. Intrarenal vasodilator prostaglandins oppose the action of angiotensin II on the renal vasculature. The use of prostaglandin synthesis inhibitors in dogs or cats with severe heart failure could potentially reduce glomerular filtration (by increasing afferent arteriolar resistance) and enhance sodium retention.

## **Renal Effects**

Renal efferent glomerular arteriolar constriction, mediated by sympathetic stimulation and angiotensin II, helps maintain glomerular filtration in the face of reduced cardiac output and renal blood flow. Higher oncotic and lower hydrostatic pressures develop in the peritubular capillaries, enhancing the reabsorption of tubular fluid and sodium. Angiotensin II—mediated aldosterone release further promotes sodium and water retention. Continued activation of these mechanisms leads to clinical edema and effusions.

Afferent arteriolar vasodilation mediated by endogenous prostaglandins and natriuretic peptides can partially offset the effects of efferent vasoconstriction, but progressive impairment of renal blood flow leads to renal insufficiency. Diuretics not only can magnify azotemia and electrolyte loss but can further reduce cardiac output and activate the neurohormonal mechanisms.

## Other Effects

Reduced exercise capacity, along with skeletal muscle atrophy, occurs in patients with heart failure. Poor diastolic filling, inadequate forward output, and pulmonary edema or pleural effusion can interfere with exercise ability. Furthermore, impaired peripheral vasodilation during exercise contributes to inadequate skeletal muscle perfusion and fatigue. Excessive peripheral sympathetic tone, angiotensin II (both circulating and locally produced), and vasopressin can contribute to impaired skeletal muscle vasodilatory capacity in patients with CHF. Increased vascular wall sodium content and interstitial fluid pressure stiffen and compress vessels. Other mechanisms can include impaired endothelium-dependent relaxation, increased endothelin concentration, and vascular wall changes induced by the growth factor effects of various neurohormonal vasoconstrictors. ACE inhibitor therapy, with or without spironolactone, may improve endothelial vasomotor function and exercise capacity. Pulmonary endothelial function is improved by ACE inhibitors in dogs with CHE.

#### GENERAL CAUSES OF HEART FAILURE

The causes of heart failure are quite diverse; it can be useful to think of them in terms of underlying pathophysiology. In most cases of heart failure, the major initiating abnormality is myocardial (systolic pump) failure, systolic pressure overload, volume overload, or reduced ventricular compliance (impaired filling). Nevertheless, several pathophysiologic abnormalities often coexist; both systolic and diastolic function abnormalities are common in patients with advanced failure.

Myocardial failure is characterized by poor ventricular contractile function, and it is most commonly secondary to idiopathic dilated cardiomyopathy; valvular insufficiency may or may not be present initially but usually develops as the affected ventricle dilates. Persistent tachyarrhythmias, some nutritional deficiencies, and other cardiac insults also can lead to myocardial failure (see Chapters 7 and 8). Diseases that cause a volume or flow overload to the heart usually involve a primary "plumbing" problem (e.g., a leaky valve or abnormal systemic-to-pulmonary connection). Cardiac pump function is often maintained at a near-normal level for a prolonged time, but myocardial contractility does eventually deteriorate (see Chapters 5 and 6). Pressure overload results when the ventricle must generate higherthan-normal systolic pressure to eject blood. Concentric hypertrophy increases ventricular wall thickness and stiffness and predisposes the patient to ischemia. Excessive pressure loads eventually lead to a decline in myocardial contractility. Myocardial pressure overload results from congenital ventricular outflow obstruction and systemic or pulmonary hypertension (see Chapters 5, 10, and 11). Diseases that restrict ventricular filling impair diastolic function. These include hypertrophic and restrictive myocardial disease and pericardial disease (see Chapters 8 and 9). Contractile ability is usually normal initially, but high filling pressure leads to congestion behind the ventricle(s) and may diminish cardiac output. Examples of common diseases are listed in Table 3-1 according to their main initiating pathophysiology and typical clinical manifestation of CHF signs.



TABLE 3-1

Common Causes of Congestive Heart Failure (CHF)

Common Causes of Congestive Heart Panule (CITY)		
MAJOR PATHOPHYSIOLOGY	TYPICAL CHF MANIFESTATION*	
Myocardial Failure		
Idiopathic dilated cardiomyopathy Myocardial ischemia/infarction Drug toxicities (e.g., doxorubicin) Infective myocarditis	Either L- or R-CHF L-CHF L-CHF Either L- or R-CHF	
Volume-Flow Overload		
Mitral valve regurgitation (degenerative, congenital, infective)	L-CHF	
Aortic regurgitation (infective endocarditis, congenital)	L-CHF	
Ventricular septal defect	L-CHF	
Patent ductus arteriosus	L-CHF	
Tricuspid valve regurgitation (degenerative, congenital, infective)	R-CHF	
Tricuspid endocarditis	R-CHF	
Chronic anemia	Either L- or R-CHF	
Thyrotoxicosis	Either L- or R-CHF	
Pressure Overload		
(Sub)aortic stenosis	L-CHF	
Systemic hypertension	L-CHF (rare)	
Pulmonic stenosis	R-CHF	
Heartworm disease	R-CHF	
Pulmonary hypertension	R-CHF	
Impaired Ventricular Filling		
Hypertrophic cardiomyopathy	L-(+/- R-) CHF	
Restrictive cardiomyopathy	L-(+/ R-) CHF	
Cardiac tamponade	R-CHF	
Constrictive pericardial disease	R-CHF	

<sup>\*</sup> L-CHF, Left-sided congestive heart failure (pulmonary edema as main congestive sign); R-CHF, right-sided congestive heart failure (pleural effusion and/or ascites as main congestive sign). Weakness and other low-output signs can occur with any of these diseases, especially those associated with arrhythmias.

# APPROACH TO TREATING HEART FAILURE

Most current treatment strategies are aimed at modifying either the results of NH activation (i.e., sodium and water retention) or the activation process itself (e.g., ACE inhibition). In most cases, therapy centers on controlling edema and effusions, improving cardiac output, reducing cardiac workload, supporting myocardial function, and managing concurrent arrhythmias. The approach to these goals varies somewhat with different diseases, most notably those causing restriction to ventricular filling.

The evolving perspective on CHF management is based on blocking excessive NH activation and preventing progression of myocardial remodeling and dysfunction, with diuretics being used to control signs of congestion. Future strategies may also involve drugs that block cytokines, antagonize endothelins, and enhance atrial peptides, as well as other strategies to block the effects of NH activation.

## Classification of Severity

Guidelines for clinical staging of heart failure (based on the American Heart Association and American College of Cardiology [AHA/ACC] system) are being increasingly applied to veterinary patients (Table 3-2). These describe disease progression through four stages over time. This staging system emphasizes the importance of early diagnosis and evidence-based management of heart dysfunction. It also deemphasizes the term "congestive" in *congestive heart failure* because volume overload is not consistently present at all stages. Nevertheless, attention to the patient's fluid status is highly important.

The clinical severity of heart failure is also sometimes described according to a modified New York Heart Association (NYHA) classification scheme or the International Small Animal Cardiac Health Council (ISACHC) criteria. These systems group patients into functional categories on the basis of clinical observations rather than underlying cardiac disease or myocardial function. Such classification can be helpful conceptually and for categorizing study patients. Forrester's classification is another method of grouping heart failure patients. Dogs with chronic mitral regurgitation often fall into group II; severe dilated cardiomyopathy is the most common diagnosis in group IV. Diseases causing group III heart failure are rare in dogs and cats. Regardless of the clinical classification scheme, identifying the underlying etiology and pathophysiology, as well as the clinical severity, is important for individualized therapy.

# TREATMENT FOR ACUTE CONGESTIVE HEART FAILURE

#### **GENERAL CONSIDERATIONS**

Fulminant CHF is characterized by severe cardiogenic pulmonary edema, with or without pleural and/or abdominal effusions or poor cardiac output. Therapy is aimed at rapidly clearing pulmonary edema, improving oxygenation, and optimizing cardiac output (Box 3-1). Thoracocentesis should



TABLE 3-2

Classification Systems for Heart Failure Severity

CLASSIFICATION	DEGREE OF SEVERITY			
Modified AHA/ACC Heart Failure Staging System				
A	Patient "at risk" for the development of heart failure, but apparent cardiac structural abnormality not yet identified			
В	Structural cardiac abnormality is evident, but no clinical signs of heart failure			
С	Structural cardiac abnormality, with past or present clinical signs of heart failure			
D	Persistent or end-stage heart failure signs, refractory to standard therapy			
Modified NYHA Functional Classification				
1	Heart disease is present but no evidence of heart failure or exercise intolerance; cardiomegaly is minimal to absent			
<del>1</del> 1	Signs of heart disease with evidence of exercise intolerance; radiographic cardiomegaly is present			
111	Signs of heart failure with normal activity or at night (e.g., cough, orthopnea); radiographic signs of significant cardiomegaly and pulmonary edema or pleural/abdominal effusion			
IV	Severe heart failure with clinical signs at rest or with minimal activity; marked radiographic signs of CHF and cardiomegaly			
International Small Animal Cardiac Health Council Functional Classification				
1	Asymptomatic patient			
la	Signs of heart disease without cardiomegaly			
1b	Signs of heart disease and evidence of compensation (cardiomegaly)			
H	Mild to moderate heart failure. Clinical signs of failure evident at rest or with mild exercise, and adversely affect quality of life			
III	Advanced heart failure. Clinical signs of CHF are immediately obvious			
Illa	Home care is possible			
IIIb	Hospitalization recommended (cardiogenic shock, life-threatening edema, large pleural effusion, refractory ascites)			
Forrester's Classification (Group)				
1	Normal cardiac output and pulmonary venous pressures			
11	Pulmonary congestion but normal cardiac output			
III	Low cardiac output and peripheral hypoperfusion with no pulmonary congestion			
IV	Low cardiac output with pulmonary congestion			

AHA/ACC, American Heart Association and American College of Cardiology; CHF, congestive heart failure.

be performed expediently if marked pleural effusion exists. Likewise, large-volume ascites should be drained to improve ventilation. Animals with severe CHF are greatly stressed. Physical activity must be maximally curtailed to reduce total oxygen consumption; cage confinement is preferred. Environmental stresses such as excess heat and humidity or extreme cold should be avoided. When transported, the animal should be placed on a cart or carried. Unnecessary handling of the patient and administration of oral medications should be avoided, when possible.

### SUPPLEMENTAL OXYGEN

Oxygen administered by face mask or improvised hood, nasal catheter, endotracheal tube, or oxygen cage is beneficial as long as the method chosen does not increase the patient's distress. An oxygen cage with temperature and humidity controls is preferred, and a setting of 65°F is recommended for normothermic animals. Oxygen flow of 6 to 10 L/min is

usually adequate. Concentrations of 50% to 100% oxygen may be needed initially, but this should be reduced within a few hours to 40% to avoid lung injury. When a nasal tube is used, humidified O<sub>2</sub> is delivered at a rate of 50 to 100 ml/kg/min. Extremely severe pulmonary edema with respiratory failure may respond to endotracheal or tracheotomy tube placement, airway suctioning, and mechanical ventilation. Positive end-expiratory pressure helps clear small airways and expand alveoli. Positive airway pressures can adversely affect hemodynamics, however, and chronic high oxygen concentrations (>70%) can injure lung tissue (see Suggested Readings for more information). Continuous monitoring is essential for intubated animals.

# **DRUG THERAPY** Diuresis

Rapid diuresis can be achieved with IV furosemide; effects begin within 5 minutes, peak by 30 minutes, and last about



## Acute Treatment of Decompensated Congestive Heart Failure

Minimize patient stress!

Cage rest/transport on gurney (no activity allowed) Improve oxygenation:

Ensure airway patency

Give supplemental  $O_2$  (avoid >50% for >24 hours)

If frothing evident, suction airways

Intubate and mechanically ventilate if necessary

Thoracocentesis if pleural effusion suspected/documented

Remove alveolar fluid:

Diuresis:

Furosemide (dogs: 2-5[-8] mg/kg IV or IM, q1-4h until respiratory rate decreases, then 1-4 mg/kg q6-12h, or 0.6-1 mg/kg/h CRI [see text]; cats: 1-2[-4] mg/kg IV or IM, q1-4h until respiratory rate decreases, then q6-12h}

Redistribute blood volume:

Vasodilators (sodium nitroprusside, if able to monitor BP closely: 0.5-1 μg/kg/min CRI in D<sub>5</sub>W, titrate upward as needed to 5-15 μg/kg/min; or 2% nitroglycerin ointment—Dogs: <sup>1</sup>/<sub>2</sub> to 1<sup>1</sup>/<sub>2</sub> inch cutaneously q6h; cats: <sup>1</sup>/<sub>4</sub> to <sup>1</sup>/<sub>2</sub> inch cutaneously q6h)

±Morphine (dogs only, see below)

±Phlebotomy (6-10 ml/kg)

Minimize bronchoconstriction:

Aminophylline (dogs: 4-8 mg/kg slow IV, IM, SC, or 6-10 mg/kg PO q6-8h; cats: 4-8 mg/kg IM, SC, PO q8-12h) or similar drug

Reduce anxiety:

Butorphanol (dogs: 0.2-0.3 mg/kg IM; cats: 0.2-

0.25 mg/kg IM); or

Morphine (dogs: 0.025-0.1 mg/kg IV boluses q2-3min to effect, or 0.1-0.5 mg/kg single IM or SC dose)

Acepromazine (cats: 0.05-0.2 mg/kg SC; or 0.05-0.1 mg/kg IM with butorphanol), or

Diazepam (cats: 2-5 mg IV; dogs: 5-10 mg IV)

Reduce afterload:

Hydralazine (if not using nitroprusside; dogs: 0.5-1.0 mg/kg PO repeated in 2-3 hr [until systolic arterial pressure is 90-110 mm Hg], then q12h; see text); or

Enalapril (0.5 mg/kg PO q12-24h) or other ACEI—avoid nitroprusside; or

Amlodipine (dogs: 0.1-0.3 mg/kg PO, q12-24h; see text)

Increase contractility (if myocardial failure present):

Dobutamine\* (1-10 μg/kg/min CRI; start low), or dopamine† (dogs: 1-10 μg/kg/min CRI; cats: 1-5 μg/kg/min CRI; start low)

Amrinone (1-3 mg/kg IV; 10-100  $\mu$ g/kg/min CRI), or milrinone (50  $\mu$ g/kg IV over 10 minutes initially; 0.375-0.75  $\mu$ g/kg/minute CRI [human dose])

Pimobendan or digoxin PO (see Table 3-3); (digoxin loading dose [see text for indications]: PO—1 or 2 doses at twice calculated maintenance; dog IV: 0.01-0.02 mg/kg—give 1/4 of this total dose in slow boluses over 2-4 hours to effect; cat IV: 0.005 mg/kg—give 1/2 of total, then 1-2 hours later give 1/4 dose bolus(es), if needed)

Monitor and address abnormalities as possible:

Respiratory rate, heart rate and rhythm, arterial pressure, O<sub>2</sub> saturation, body weight, urine output, hydration, attitude, serum biochemistry and blood gas analyses, and pulmonary capillary wedge pressure (if available)

Diastolic dysfunction (e.g., cats with hypertrophic cardiomyopathy):

General recommendations, O<sub>2</sub> therapy, and furosemide as above

± Nitroglycerin and mild sedation

Consider IV esmolol (200-500 µg/kg IV over 1 minute, followed by 25-200 µg/kg CRI) or diltiazem (0.15-0.25 mg/kg over 2-3 minutes IV)

ACE, Angiotensin-converting enzyme; CRI, constant rate infusion;  $D_5W$ , 5% dextrose in water.

2 hours. This route also provides a mild venodilating effect. Some patients require aggressive initial doses or cumulative doses administered at frequent intervals (see Box 3-1). Furosemide can be given by constant rate infusion (CRI), which may provide greater diuresis than bolus injection. The veterinary formulation (50 mg/ml) can be diluted to 10 mg/ml for CRI using 5% dextrose in water (D₅W), lactated Ringer's solution (LRS), or sterile water. Dilution to 5 mg/ml in D₅W or sterile water is also described. The patient's respiratory rate, as well as other parameters (discussed in more detail later), guide the intensity of continued furosemide therapy. Once diuresis has begun and respiration improves, the dosage is reduced to prevent excessive volume contraction

or electrolyte depletion. An ancillary approach that has been described for patients with fulminant cardiogenic edema is phlebotomy (up to 25% of total blood volume), but this is not generally done.

#### Vasodilation

Vasodilator drugs can reduce pulmonary edema by increasing systemic venous capacitance, lowering pulmonary venous pressure, and reducing systemic arterial resistance. Although ACE inhibitors are a mainstay of CHF management, more immediate afterload reduction is desirable for animals with acute pulmonary edema. Arteriolar vasodilation is not recommended for heart failure

<sup>\*</sup>Dilution of 250 mg dobutamine into 500 ml of D<sub>5</sub>W or lactated Ringer's solution yields a solution of 500 μg/ml; CRI of 0.6 ml/kg/hr provides 5 μg/kg/min.

<sup>†</sup>Dilution of 40 mg of dopamine into 500 ml of D5W or lactated Ringer's solution yields a solution of 80 µg/ml; a volume of 0.75 ml/kg/hr provides 1 µg/kg/min.

caused by diastolic dysfunction or ventricular outflow obstruction.

Sodium nitroprusside is a potent arteriolar and venous dilator, with direct action on vascular smooth muscle. It is given by IV infusion because of its short duration of action. Blood pressure must be closely monitored when using this drug. The dose is titrated to maintain mean arterial pressure at about 80 mm Hg (at least >70 mm Hg) or systolic blood pressure between 90 and 110 mm Hg. Nitroprusside CRI is usually continued for 12 to 24 hours. Dosage adjustments may be needed because drug tolerance develops rapidly. Profound hypotension is the major adverse effect. Cyanide toxicity can result from excessive or prolonged use (e.g., longer than 48 hours). Nitroprusside should not be infused with other drugs, and should be protected from light.

Hydralazine, a pure arteriolar dilator, is an alternative to nitroprusside. It is useful for refractory pulmonary edema caused by mitral regurgitation (and sometimes dilated cardiomyopathy) because it can reduce regurgitant flow and lower left atrial pressure. An initial dose of 0.75 to 1 mg/kg is given orally, followed by repeated doses every 2 to 3 hours until the systolic blood pressure is between 90 and 110 mm Hg or clinical improvement is obvious. If blood pressure cannot be monitored, an initial dose of 1 mg/kg is repeated in 2 to 4 hours if sufficient clinical improvement has not been observed. The addition of 2% nitroglycerin ointment may provide beneficial venodilating effects.

An ACE inhibitor or amlodipine, with or without nitroglycerin ointment, is an alternative to hydralazine/nitroglycerine. The onset of action is slower and the effects are less pronounced, but this regimen can still be helpful.

Nitroglycerin (and other orally or transcutaneously administered nitrates) act mainly on venous smooth muscle to increase venous capacitance and reduce cardiac filling pressure. The major indication for nitroglycerin is acute cardiogenic pulmonary edema. Nitroglycerin ointment (2%) is usually applied to the skin of the groin, axillary area, or ear pinna, although the efficacy of this in heart failure is unclear. An application paper or glove is used to avoid skin contact by the person applying the drug.

## Other Acute Therapy

Some dogs with severe pulmonary edema and bronchoconstriction benefit from bronchodilator therapy. Aminophylline, given by slow IV administration or intramuscular (IM) injection, has mild diuretic and positive inotropic actions as well as a bronchodilating effect; it also decreases fatigue of respiratory muscles. Adverse effects include increased sympathomimetic activity and arrhythmias. The oral route can be used when respiration improves because gastrointestinal (GI) absorption is rapid.

Mild sedation (butorphanol or morphine for dogs, butorphanol with acepromazine for cats) can reduce anxiety. Because morphine can induce vomiting, butorphanol may be a better choice in dogs. Nevertheless, other beneficial effects of morphine include slower, deeper breathing from respiratory center depression and redistribution of blood

away from the lungs via dilation of capacitance vessels. Morphine is contraindicated in dogs with neurogenic edema because it can raise intracranial pressure. Morphine is not used in cats.

## **Inotropic Support**

Positive inotropic therapy is indicated when heart failure is caused by poor myocardial contractility. Oral therapy with pimobendan or digoxin can be started as soon as practical for animals needing chronic inotropic support (see Table 3-3 and p. 65). Treatment for one to three days with an IV sympathomimetic (catecholamine) or phosphodiesterase (PDE) inhibitor drug can help support arterial pressure, forward cardiac output, and organ perfusion when myocardial failure or hypotension is severe.

Catecholamines enhance contractility via a cAMP-mediated increase in intracellular Ca<sup>++</sup>. They can provoke arrhythmias and increase pulmonary and systemic vascular resistance (potentially exacerbating edema formation). Their short half-life (<2 minutes) and extensive hepatic metabolism necessitate constant IV infusion. Dobutamine (a synthetic analog of dopamine) has lesser effect on heart rate and afterload and is preferred over dopamine. Dobutamine stimulates  $\beta_1$ -receptors, with only weak action on  $\beta_2$ - and  $\alpha$ -receptors. Lower doses (e.g., 3 to 7 µg/kg/min) have minimal effects on heart rate and blood pressure. The initial infusion rate should be low; this can be gradually increased over hours to achieve greater inotropic effect and maintain systolic arterial pressure between 90 and 120 mm Hg. Heart rate, rhythm, and blood pressure must be monitored closely. Although dobutamine is less arrhythmogenic than other catecholamines, higher infusion rates (e.g., 10 to 20 µg/kg/min) can precipitate supraventricular and ventricular arrhythmias. Adverse effects are more likely in cats; these include seizures at relatively low doses.

Dopamine at low doses (<2-5  $\mu$ g/kg/minute) also stimulates vasodilator dopaminergic receptors in some regional circulations. Low-to-moderate doses enhance contractility and cardiac output, but high doses (10-15  $\mu$ g/kg/minute) cause peripheral vasoconstriction and increase heart rate, O<sub>2</sub> consumption, and the risk of ventricular arrhythmias. An initial IV infusion of 1  $\mu$ g/kg/min can be titrated upward to desired clinical effect. The infusion rate should be decreased if sinus tachycardia or other tachyarrhythmias develop.

Bipyridine PDE inhibitors such as amrinone and milrinone increase intracellular Ca<sup>++</sup> by inhibiting PDE III, an intracellular enzyme that degrades cAMP. These drugs also cause vasodilation, as increased cAMP promotes vascular smooth muscle relaxation. Hypotension, tachycardia, and GI signs can occur when giving high doses. These drugs can exacerbate ventricular arrhythmias. The effects of amrinone are short-lived (<30 minutes) after IV injection in normal dogs, so CRI is required for sustained effect. Peak effects occur after 45 minutes of CRI in dogs. Amrinone is sometimes used as an initial slow IV bolus followed by CRI; half the original bolus dose can be repeated after 20 or 30 minutes. Milrinone has a much greater potency than amrinone, but



#### Drugs for Managing Chronic Heart Failure

DRUG	DOGS	CATS
Diuretics		
Furosemide	1-3 mg/kg PO q8-24h (long term); use smallest effective dose	1-2 mg/kg PO q8-12h; use smallest effective dose
Spironolactone	0.5-2 mg/kg PO q(12-)24h	0.5-1 mg/kg PO q(12-)24h
Chlorothiazide	20-40 mg/kg PO q12h	20-40 mg/kg PO q12h
Hydrochlorothiazide	2-4 mg/kg PO q12h	1-2 mg/kg PO q12h
ACE Inhibitors		
Enalapril	0.5 mg/kg PO q(12-)24h	0.25-0.5 mg/kg PO q24(-12)h
Benazepril	0.25-0.5 mg/kg PO q(12-)24h	0.25-0.5 mg/kg PO q24(-12)h
Captopril	0.5-2.0 mg/kg PO q8-12h (low initial dose)	0.5-1.25 mg/kg PO q12-24h
Lisinopril Fosinopril	0.25-0.5 mg/kg PO q(12-)24h 0.25-0.5 mg/kg PO q24h	0.25-0.5 mg/kg PO q24h
Ramipril	0.125-0.25 mg/kg PO q24h	_
Imidapril	0.25 mg/kg PO q24h	_
Other Vasodilators		
Hydralazine Amlodipine Prazosin	0.5-2 mg/kg PO q12h (to 1 mg/kg initial) 0.05 (initial) to 0.3(-0.5) mg/kg PO q(12-)24h Medium dogs: 1 mg PO q8-12hr; large dogs:	2.5 (up to 10) mg/cat PO q12h 0.3125-0.625 mg/cat PO q24(-12)h
110203111	2 mg PO q8h	
Nitroglycerin 2% ointment	1/2- $11/2$ inch cutaneously q4-6h	$^{1}/_{4}$ - $^{1}/_{2}$ inch cutaneously q4-6h
Isosorbide dinitrate	0.5-2 mg/kg PO q(8-)12h	_
Isosorbide mononitrate	0.25-2 mg/kg PO q12h	_
Positive Inotropes		
Pimobendan	0.1-0.3 mg/kg PO q12h, start low; give at least 1 hour before feeding	
Digoxin	PO: dogs <22 kg, 0.005-0.008 mg/kg q12h; dogs >22 kg, 0.22 mg/m² or 0.003-0.005 mg/kg q12h. Decrease by 10% for elixir. Maximum: 0.5 mg/day or 0.375 mg/day for Doberman Pinchers. See Box 3-1 for loading doses.	0.007 mg/kg (or 1/4 of 0.125 mg tab) PO q48h. See Box 3-1 for IV dose.

CRI, Constant rate infusion.

there is little veterinary data with the IV form. A PDE inhibitor can be used concurrently with digoxin and a catecholamine.

Digoxin is generally not used intravenously except for some supraventricular tachyarrhythmias when other acute therapy is unavailable or ineffective (see Chapter 4). Acidosis and hypoxemia associated with severe pulmonary edema can increase myocardial sensitivity to digitalis-induced arrhythmias. If digoxin is used intravenously, it must be given slowly (over at least 15 minutes); rapid injection causes peripheral vasoconstriction. The calculated dose is usually divided, and boluses of one fourth the dose are given slowly over several hours.

If arrhythmias develop during IV inotropic therapy, the infusion rate is reduced or the drug is discontinued. In animals with atrial fibrillation, catecholamine infusion is

likely to increase the ventricular response rate by enhancing atrioventricular (AV) conduction. If dobutamine or dopamine is deemed necessary for such a case, diltiazem (administered rapidly by mouth or cautiously by IV) is used to reduce the heart rate. Digoxin, administered either by mouth (loading) or cautiously by IV, is an alternative.

# HEART FAILURE CAUSED BY DIASTOLIC DYSFUNCTION

When acute CHF is caused by hypertrophic cardiomyopathy, thoracocentesis (if needed), diuretics, and oxygen therapy are given as outlined previously. Cutaneous nitroglycerin can also be used. Diltiazem or a  $\beta_1$ -blocker such as atenolol can be given to slow heart rate and increase ventricular filling time once severe dyspnea has abated; alternatively, IV administration of diltiazem or esmolol could be used. Propranolol

(or other nonselective  $\beta$ -blockers) is generally avoided in patients with fulminant pulmonary edema because  $\beta_2$ -blockade could induce bronchoconstriction.

Arteriolar vasodilators can be detrimental if dynamic left ventricular (IV) outflow obstruction coexists, because afterload reduction provokes greater systolic obstruction (see Chapter 8). ACE inhibitors at standard doses do not appear to worsen the IV outflow gradient. Addition of an ACE inhibitor is recommended as soon as oral therapy is possible.

### MONITORING AND FOLLOW-UP

Repeated assessment is important to monitor the effectiveness of therapy and to prevent hypotension or severe azotemia caused by excessive diuresis. Mild azotemia commonly occurs. Hypokalemia and metabolic alkalosis can occur after aggressive diuresis. A serum potassium concentration within the mid- to high-normal range is especially important for animals with arrhythmias. Serum biochemical testing every 24 to 48 hours is advised until the patient is eating and drinking well.

Arterial blood pressure can be monitored indirectly or directly, but gaining arterial access can increase patient stress. Indirect measures of organ perfusion such as capillary refill time, mucous membrane color, urine output, toe-web temperature, and mentation can also be useful. Body weight should be monitored, especially with aggressive diuretic therapy.

Central venous pressure (CVP) does not adequately reflect left heart filling pressures. It should not be used to guide diuretic or fluid therapy in patients with cardiogenic pulmonary edema. Although pulmonary capillary wedge pressure can reliably guide therapy, the placement and care of an indwelling pulmonary artery catheter require meticulous attention to asepsis and close monitoring.

Pulse oximetry is a helpful noninvasive means of monitoring oxygen saturation (SpO<sub>2</sub>). Supplemental O<sub>2</sub> should be given if SpO<sub>2</sub> is <90%; mechanical ventilation is indicated if SpO<sub>2</sub> is <80% despite O<sub>2</sub> therapy. Arterial sampling for blood gas analysis is more accurate but is stressful for the patient. Resolution of radiographic evidence for pulmonary edema usually lags behind clinical improvement by a day or two.

After respiratory signs begin to abate and diuresis is evident, low-sodium water is offered. Fluid administration (either subcutaneously or intravenously) is generally not advised in patients with fulminant CHF. In most cases, gradual rehydration by free choice (low sodium) water intake is preferred even after aggressive diuretic therapy. However, fluid therapy may be necessary for patients with heart failure and renal failure, marked hypokalemia, hypotension, digoxin toxicity, persistent anorexia, or other serious systemic disease. Some animals require relatively high cardiac filling pressure to maintain cardiac output, especially those with myocardial failure or markedly reduced ventricular compliance (e.g., from hypertrophic cardiomyopathy or pericardial disease). Diuresis and vasodilation in such cases can cause inadequate cardiac output and hypotension.

In most patients with decompensated CHF, the smallest fluid volume possible should be used to deliver drugs by CRI. Careful monitoring and continued diuretic use is important to prevent recurrent pulmonary edema. When additional fluid therapy is necessary, D<sub>5</sub>W or a reduced sodium fluid (e.g., 0.45% NaCl with 2.5% dextrose) with added KCl is administered at a conservative rate (e.g., 15 to 30 ml/kg/day IV). Alternatively, 0.45% NaCl with 2.5% dextrose or lactated Ringer's solution can be administered subcutaneously.

Potassium supplementation at a maintenance rate is provided by 0.05 to 0.1 mEq/kg/hour (or more conservatively, 0.5 to 2.0 mEq/kg/day). For animals with hypokalemia, higher rates are used: 0.15 to 0.2 mEq/kg/hour for mild K deficiency; 0.25 to 0.3 mEq/kg/hour for moderate deficiency; and 0.4 to 0.5 mEq/kg/hour for severe deficiency. Measuring serum K' concentration in 4 to 6 hours is advised when supplementing for moderate to severe deficiency. Hyponatremia and worsened fluid retention can develop after using low-sodium IV solutions in some patients. These require a more balanced crystalloid solution. Other supportive therapies for CHF and any underlying disease(s) depend on individual patient needs. Parenteral fluid administration is tapered off as the animal is able to resume oral food and water intake.

# MANAGEMENT OF CHRONIC HEART FAILURE

## **GENERAL CONSIDERATIONS**

A general approach to chronic heart failure therapy is presented in this section. Additional information is found in the chapters describing different diseases. Therapy is tailored to the individual animal's needs by adjusting dosages, adding or substituting drugs, and modifying lifestyle or diet. Pleural effusion and large-volume ascites that accumulate despite medical therapy should be drained to facilitate respiration. Likewise, pericardial effusion that compromises cardiac filling must be drained. As heart disease progresses, more aggressive therapy is usually needed. Support of cardiac function with digoxin or pimobendan is often indicated in dogs and sometimes in cats.

Exercise restriction helps reduce cardiac workload regardless of heart failure etiology. Strenuous exercise can provoke dyspnea and potentially serious cardiac arrhythmias even in animals with compensated CHE. Chronic heart failure is associated with skeletal muscle changes that lead to fatigue and dyspnea. Physical training can improve cardiopulmonary function and quality of life in patients with chronic heart failure. This is partly mediated by improvement in vascular endothelial function and restoration of flow-dependent vasodilation. Although it is difficult to know how much exercise is best, regular (not sporadic) mild to moderate activity is encouraged, as long as excessive respiratory effort is not induced. Bursts of strenuous activity should be avoided. Dietary salt restriction and other nutritional issues are also

important in the management of patients with chronic heart failure.

#### **DIURETICS**

Diuretic therapy is indicated for controlling cardiogenic pulmonary edema and effusions. Diuretics remain fundamental to the management of CHF because of their ability to decrease venous congestion and fluid accumulation (see Table 3-3). Agents that interfere with ion transport in the loop of Henle (e.g., furosemide) have potent ability to promote both salt and water loss. Diuretics of other classes, such as thiazides and potassium-sparing agents, are sometimes combined with furosemide for chronic heart failure therapy. Given to excess, diuretics promote excessive volume contraction and activate the renin-angiotensin-aldosterone cascade. Diuretics also can exacerbate preexisting dehydration or azotemia. Therefore the indication for their use in such animals should be clearly established, and the lowest effective dose should be used.

#### **Furosemide**

Furosemide is the loop diuretic used most widely for cats and dogs with heart failure. It acts on the ascending limb of the loop of Henle to inhibit active Cl<sup>-</sup>, K<sup>+</sup>, and Na<sup>-</sup> cotransport, thereby promoting excretion of these electrolytes; Ca<sup>++</sup> and Mg<sup>-+</sup> are also lost in the urine. Loop diuretics can increase systemic venous capacitance, possibly by mediating renal prostaglandin release. Furosemide may also promote salt loss by increasing total renal blood flow and by preferentially enhancing renal cortical flow. The loop diuretics are well absorbed when given orally. After oral administration, diuresis occurs within 1 hour, peaks between 1 to 2 hours, and may last for 6 hours. Furosemide is highly protein bound; about 80% is actively secreted unchanged in the proximal renal tubules, with the remainder excreted as glucuronide.

Although aggressive furosemide treatment is indicated for acute, fulminant pulmonary edema, the smallest effective doses should be used for chronic heart failure therapy. The dosage varies, depending on the clinical situation. Respiratory pattern, hydration, body weight, exercise tolerance, renal function, and serum electrolyte concentrations are used to monitor response to therapy. Furosemide (or other diuretic) alone is not recommended as the sole treatment for chronic heart failure because it can exacerbate NH activation and reduce renal function.

Adverse effects are usually related to excessive fluid and/or electrolyte losses. Because they are more sensitive than dogs, lower doses are used in cats. Although hypokalemia is the most common electrolyte disturbance, it is unusual in dogs that are not anorexic. Hyponatremia develops in some patients with severe CHF and results from an inability to excrete free water (dilutional hyponatremia) rather than from a total body sodium deficit.

## **Spironolactone**

Spironolactone may be a useful adjunct therapy in patients with chronic refractory heart failure. Its anti-aldosterone

effects are also thought to be important locally within the heart. Spironolactone is a competitive antagonist of aldosterone. It promotes Na\* loss and K\* retention in the distal renal tubule and can reduce the renal potassium wasting of furosemide and other diuretics, especially when circulating aldosterone concentration is high. But its diuretic effect in normal dogs is questionable. Spironolactone's onset of action is slow; peak effect occurs within 2 to 3 days.

Aldosterone release can occur despite the use of an ACE inhibitor (so-called aldosterone escape); this may involve reduced hepatic clearance, increased release stimulated by K<sup>+</sup> elevation or Na<sup>+</sup> depletion, and local tissue aldosterone production. Spironolactone's anti-aldosterone effect is thought to mitigate aldosterone-induced cardiovascular remodeling in some cases. The drug has improved survival in people with moderate to severe CHF, but it is not yet clear whether similar survival benefit occurs clinically in dogs and cats.

A potassium-sparing diuretic must be used cautiously in patients receiving an ACE inhibitor or potassium supplement and is absolutely contraindicated in hyperkalemic patients. Adverse effects relate to excess K<sup>+</sup> retention and GI disturbances. Spironolactone may decrease digoxin clearance.

### **Thiazide Diuretics**

Thiazide diuretics decrease Na and Cl absorption and increase Ca absorption in the distal convoluted tubules. Mild to moderate diuresis with excretion of Na , Cl , K , and Mg results. The thiazides decrease renal blood flow and should not be used in azotemic animals. Adverse effects are uncommon in the absence of azotemia, but hypokalemia or other electrolyte disturbance and dehydration can occur with excessive use or in anorectic patients. Thiazides can cause hyperglycemia in diabetic or prediabetic animals by inhibiting conversion of proinsulin to insulin. Chlorothiazide's effects begin within 1 hour, peak at 4 hours, and last 6 to 12 hours. Hydrochlorothiazide produces diuresis within 2 hours, with peak effect at 4 hours, and duration of about 12 hours.

# ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors (ACEIs) are indicated for most causes of chronic heart failure, especially dilated cardiomyopathy and chronic valvular insufficiency (see Table 3-3). Their use has led to clinical improvement and lowered mortality rates in people with heart failure; similar benefits seem to occur in dogs with myocardial failure or volume overload and in cats with diastolic dysfunction. They moderate excess NH responses in several ways; therefore ACEIs have considerable advantages over hydralazine and other arteriolar dilators. ACEIs have only modest diuretic and vasodilatory effects; their main benefits arise from opposing the effects of NH activation and abnormal cardiovascular remodeling changes. By blocking the formation of angiotensin II, ACEIs allow arteriolar and venous vasodilation. The secondary inhibition of aldosterone release helps reduce Na<sup>+</sup> and water retention

and therefore edema/effusions, as well as the adverse effects of aldosterone directly on the heart. ACEIs reduce ventricular arrhythmias and the rate of sudden death in people (and probably animals) with heart failure, likely because angiotensin II—induced facilitation of norepinephrine and epinephrine release is inhibited. Their vasodilating effects may be enhanced by vasodilator kinins normally degraded by ACE. A local vasodilating effect may occur through inhibition of ACE found within vascular walls, even in the absence of high circulating renin concentrations. Local ACE inhibition may be beneficial by modulating vascular smooth muscle and myocardial remodeling. However, it is unclear whether ACE inhibitors prevent ventricular remodeling and dilation in dogs with heart disease. ACE inhibitors have been variably effective in treating dogs with hypertension.

Most ACEIs (except captopril and lisinopril) are prodrugs that are converted to their active form in the liver; therefore severe liver dysfunction can interfere with this conversion. Adverse effects of ACEIs include hypotension, GI upset, deterioration of renal function, and hyperkalemia (especially when used with a potassium-sparing diuretic or potassium supplement). Angiotensin II is important in mediating renal efferent arteriolar constriction, which maintains glomerular filtration when renal blood flow decreases. As long as cardiac output and renal perfusion improve with therapy, renal function is usually maintained. Poor glomerular filtration is more likely to result with overdiuresis, excess vasodilation, or severe myocardial dysfunction. Azotemia is first addressed by decreasing the diuretic dosage. If necessary, the ACEI dosage is decreased or discontinued. Hypotension can usually be avoided by starting with low initial doses. Other adverse effects reported in people include rash, pruritus, impairment of taste, proteinuria, cough, and neutropenia. The mechanism of ACEI-induced cough in people is unclear but may involve inhibition of endogenous bradykinin degradation or may be associated with increased NO generation. NO has an inflammatory effect on bronchial epithelial cells.

## **Enalapril**

Enalapril maleate is absorbed well when taken orally; administration with food does not decrease its bioavailability. It is hydrolyzed in the liver to enalaprilat, its most active form. Peak ACE-inhibiting activity occurs within 4 to 6 hours in dogs. Duration of action is 12 to 14 hours, and effects are minimal by 24 hours at the recommended once-daily dose. Enalapril is generally administered once daily, although some dogs respond better when dosed every 12 hours. In cats maximal activity occurs within 2 to 4 hours after an oral dose of either 0.25 or 0.5 mg/kg; some ACE inhibition (50% of control) persists for two to three days. Enalapril and its active metabolite are excreted in the urine. Renal failure and severe CHF prolong its half-life, so reduced doses or benazepril are used in such patients. Severe liver dysfunction will interfere with the conversion of the prodrug to the active enalaprilat; lisinopril or captopril should be considered in such patients instead. Injectable enalaprilat is also available, but little veterinary data exist on its use; this form is not well absorbed orally.

## Benazepril

Benazepril is metabolized to its active form, benazeprilat. Only about 40% is absorbed when administered orally, but feeding does not affect absorption. After oral administration, peak ACE inhibition occurs within 2 hours in dogs and cats; its effect can last over 24 hours. In cats doses of 0.25 to 0.5 mg/kg result in 100% inhibition of ACE that is maintained at >90% for 24 hours, and tapers off to about 80% by 36 hours. Benazapril has an initial half-life of 2.4 hours and terminal half-life of about 29 hours in cats. Repeated doses produce moderate increases in drug plasma concentration. Benazepril is a preferred ACEI for animals with renal disease. This drug is climinated equally in urine and bile in dogs. In cats about 85% of the drug is excreted in the feces and only 15% in urine. The drug is generally well tolerated. It may also slow renal function deterioration in cats with kidney disease.

## Captopril

Captopril was the first ACEI used clinically. Captopril contains a sulfhydryl group, in contrast to enalapril and others. Disulfide metabolites can act as free radical scavengers. This might have beneficial effects for the treatment of some heart diseases, although the clinical significance is presently unclear. Captopril appears to be less effective than several other agents in reducing ACE activity in normal dogs. Captopril is well absorbed when taken orally (75% bioavailable); however, food decreases its bioavailability by 30% to 40%. In dogs hemodynamic effects appear within 1 hour, peak in 1 to 2 hours, and last less than 4 hours. Captopril is excreted in the urine.

### Lisinopril

Lisinopril is a lysine analog of enalaprilat with direct ACE-inhibiting effects. It is 25% to 50% bioavailable, and absorption is not affected by feeding. The time to peak effect is 6 to 8 hours. The duration of ACE inhibition appears long, but more specific information in animals is lacking. Once-daily administration has been tried with apparent effectiveness.

## **Fosinopril**

Fosinopril is structurally different in that it contains a phosphinic acid radical (rather than sulfhydryl or carboxyl), and it may be retained longer in myocytes. Fosinopril is also a prodrug that is converted to the active fosinoprilat in the GI mucosa and liver. Elimination occurs equally between kidney and liver; compensatory increases in one pathway occur with impairment of the other. Its duration of action is well over 24 hours in people. Fosinopril may cause falsely low scrum digoxin measurements using certain RIA assays.

## Other Angiotensin-Converting Enzyme Inhibitors

Other agents that have been used in animals with heart failure include ramipril, quinipril, and imidapril. The latter is comparable to enalapril in efficacy and is available in liquid form, although other ACEIs can be compounded into suspension.

#### POSITIVE INOTROPIC AGENTS

A positive inotropic agent is indicated for patients with dilated cardiomyopathy or other causes of myocardial failure, including dogs with advanced mitral regurgitation (see Table 3-3). Pimobendan, now approved in the United States, and digoxin are the inotropic agents available for chronic oral therapy. Pimobendan improves cardiac pump function both by enhancing contractility as well as by vasodilation. Digoxin is still used in some cases and can be combined with pimobendan. Digoxin also is indicated for treating some supraventricular tachyarrhythmias (see Chapter 4), except in cats with hypertrophic cardiomyopathy.

#### Pimobendan

Pimobendan (Vetmedin) is a benzimidazole-derivative phosphodiesterase III inhibitor. It slows cAMP breakdown and enhances adrenergic effects on Ca++ fluxes and myocardial contractility. Pimobendan also has a calcium-sensitizing effect on the contractile proteins, which promotes increased contractility without an increase in myocardial O2 requirement. Pimobendan is known as an inodilator because it increases contractility while also causing systemic and pulmonary vasodilation. The drug may have other beneficial effects by modulating NH and proinflammatory cytokine activation. Peak plasma concentrations occur within an hour of oral dosing. Bioavailability is about 60% in dogs, but this decreases in the presence of food. Pimobendan is highly protein bound. Elimination is mainly via hepatic metabolism and biliary excretion. Concurrent Ca<sup>++</sup> or β-blocker therapy may diminish the drug's positive inotropic effect.

Clinical improvement has occurred in many dogs when this agent was added to conventional CHF therapy (e.g., furosemide, an ACE inhibitor, and digoxin). Pimobendan appears to improve clinical status and increase survival time in dogs with dilated cardiomyopathy (DCM) or chronic mitral valve disease. Pimobendan does not appear to increase the frequency of ventricular arrhythmias and sudden death, as has occurred with other phosphodiesterase inhibitors. There are limited anecdotal reports of pimobendan use in cats.

#### Digoxin

The benefits of digoxin arise from its modest positive inotropic effect as well as its supraventricular antiarrhythmic activity. Its ability to sensitize baroreceptors and thereby modulate neurohormonal activation is probably its most important attribute in patients with heart failure. Because digoxin is potentially toxic, low doses are used and serum concentrations should be monitored. Serum concentrations in the low to mid therapeutic range are desired (discussed in more detail later).

Digoxin is indicated in patients with heart failure caused by myocardial dysfunction, chronic mitral insufficiency, and other chronic volume or pressure overloads. Digoxin is usually contraindicated in patients with hypertrophic cardiomyopathy, especially those with ventricular outflow obstruction; it is not useful in dogs or cats with pericardial diseases. Digoxin is only moderately effective in slowing the ventricular response rate to atrial fibrillation and does not cause conversion to sinus rhythm. It is usually contraindicated when sinus or AV node disease is present. Digoxin is relatively contraindicated in most patients with serious ventricular arrhythmias because it can exacerbate such arrhythmias.

Digoxin, in addition to other digitalis glycosides, increases the Ca<sup>++</sup> available to contractile proteins by competitively binding and inhibiting the Na<sup>+</sup>, K<sup>+</sup>-ATPase pump at the myocardial cell membrane. Intracellular Na<sup>+</sup> accumulation then promotes Ca<sup>++</sup> entry via the sodium-calcium exchange. In diseased myocardial cells in which diastolic sequestration and systolic release of Ca<sup>++</sup> is impaired, digitalis glycosides may be ineffective as inotropic agents and could predispose the patient to cellular Ca<sup>++</sup> overload and electrical instability.

The antiarrhythmic effects of digoxin are mediated primarily via increased parasympathetic tone to the sinus and AV nodes and the atria. Some direct effects further prolong conduction time and refractory period of the AV node. Sinus rate slowing, reduced ventricular response rate to atrial fibrillation and flutter, and suppression of atrial premature depolarizations are resulting effects. Although some ventricular arrhythmias might be suppressed (probably via enhanced vagal tone), the digitalis glycosides have potential arrhythmogenic effects, especially in patients with heart failure.

Oral maintenance doses of digoxin are used to initiate therapy in most cases because loading doses can result in toxic serum concentrations. When more rapid achievement of therapeutic serum concentrations is important (e.g., for supraventricular tachyarrhythmia), the drug can be given at twice the oral maintenance dose for 1 to 2 doses or intravenously with caution (see Table 3-3). But alternate IV therapy for supraventricular tachycardia is usually more effective (see Chapter 4). Other IV-positive inotropic drugs (see p. 60 and Box 3-1) are safer and more effective than digoxin for immediate support of myocardial contractility.

Digoxin is well absorbed orally and undergoes minimal hepatic metabolism. Absorption is approximately 60% for the tablet form and 75% for the elixir. Bioavailability is decreased by kaolin-pectin compounds, antacids, the presence of food, and malabsorption syndromes. About 27% of the drug in serum is protein bound. The serum half-life in dogs ranges from 23 to 39 hours; therapeutic serum concentrations are achieved within 2 to 4½ days with dosing every 12 hours. In cats the reported serum half-life ranges widely, from about 25 to over 78 hours; chronic oral administration increases the half-life. The alcohol-based elixir, which is poorly palatable, results in serum concentrations approximately 50% higher than the tablet form of digoxin. Administration of the tablets with food has resulted in serum

concentrations about 50% lower than in the fasted state in cats. The pharmacokinetics in cats with heart failure are similar to those in control cats receiving aspirin, furosemide, and a low-salt diet, although much interpatient variation is present. Digoxin treatment every 48 hours in cats produces effective serum concentrations, with steady state achieved in about 10 days. Because approximately 50% of cats become toxic at a dose of 0.01 mg/kg every 48 hours, a dose of 0.007 mg/kg every 48 hours has been recommended. Serum concentrations can be measured 8 hours postdosing once steady state is reached (after about 10 days). Digoxin elimination is primarily by glomerular filtration and renal secretion in dogs, although approximately 15% is metabolized by the liver. Renal and hepatic elimination appear equally important in cats.

Serum digoxin concentration (and risk of toxicity) increases with renal failure because of reduced clearance and volume of distribution. There appears to be no correlation between the degree of azotemia and the serum digoxin concentration in dogs, making extrapolations from human formulas for calculating drug dosage in renal failure unusable in this species. Lower doses and close monitoring of serum digoxin concentration are recommended in animals with renal disease.

There is only a weak correlation between digoxin dose and serum concentration in dogs with heart failure, indicating that other factors influence the serum concentrations of this drug. Because much of the drug is bound to skeletal muscle, animals with reduced muscle mass or cachexia and those with compromised renal function can easily become toxic at the usual calculated doses. The dose should be based on the patient's calculated lean body weight because digoxin has poor lipid solubility. This consideration is especially important in obese animals. Management of digoxin toxicity is outlined later in this section. Conservative dosing and measurement of serum digoxin concentrations help to prevent toxicity.

Measurement of serum concentration is recommended 7 to 10 days after initiation of therapy (or dosage change). Samples should be drawn 8 to 10 hours postdose. Many veterinary and most human hospital laboratories can provide this service. The therapeutic serum concentration range is 1 to 2 (or 2.4) ng/ml. If the serum concentration is less than 0.8 ng/ml, the digoxin dose can be increased by 25% to 30% and the serum concentration measured the following week. But a serum concentration in the mid to low therapeutic range is probably safer. People with high-normal serum digoxin concentrations have greater risk for sudden death. If serum concentrations cannot be measured and toxicity is suspected, the drug should be discontinued for one to two days and then reinstituted at half of the original dose.

Certain drugs affect serum digoxin concentrations when administered concurrently. Quinidine increases serum digoxin concentrations by displacing the drug from skeletal muscle binding sites and reducing its renal clearance. This drug combination is therefore not recommended, but, if both must be used, the digoxin dose is reduced by 50% initially and guided by serum concentration measurement. Other drugs known to increase serum digoxin concentration include verapamil and amiodarone. Diltiazem, prazosin, spironolactone, and triamterene possibly increase serum digoxin concentration. Hypokalemia especially, as well as other electrolyte and thyroid disturbances, can potentiate digoxin toxicity. Drugs affecting hepatic microsomal enzymes may also have effects on digoxin metabolism.

## **Digoxin Toxicity**

As discussed previously, azotemia, hypokalemia, or concurrent use of certain drugs predispose the patient to digoxin toxicity. Therefore it is important to monitor renal function and serum electrolytes during digoxin therapy. Hypokalemia predisposes the patient to myocardial toxicity by leaving more available binding sites on membrane Nat, K+-ATPase for digitalis; conversely, hyperkalemia displaces digitalis from those binding sites. Hypercalcemia and hypernatremia potentiate both the inotropic and the toxic effects of the drug. Abnormal thyroid hormone concentrations can also influence the response to digoxin. Hyperthyroidism may potentiate the myocardial effects of the drug, whereas hypothyroidism prolongs the half-life of digoxin in people but has no pharmacokinetic effect in dogs. Hypoxia sensitizes the myocardium to the toxic effects of digitalis. Quinidine increases serum digoxin concentration by reducing renal clearance and competing for Na/K binding sites in skeletal muscle. Verapamil and amiodarone also increase serum digoxin concentration; other drugs that may do so include diltiazem, prazosin, and spironolactone. In addition, alteration of hepatic and renal function may affect the clearance of these drugs.

Digoxin toxicity causes GI, myocardial, or sometimes central nervous system (CNS) signs. GI toxicity may develop before signs of myocardial toxicity. Signs include anorexia, depression, vomiting, borborygmi, and diarrhea. Some of these GI signs result from the direct effects of digitalis on chemoreceptors in the area postrema of the medulla. CNS signs include depression and disorientation.

Myocardial toxicity from digitalis glycosides can cause almost any cardiac rhythm disturbance, including ventricular tachyarrhythmias, supraventricular premature complexes and tachycardia, sinus arrest, Mobitz type I second-degree AV block, and junctional rhythms. Myocardial toxicity can occur before any other signs and can lead to collapse and death, especially in animals with myocardial failure. Therefore the appearance of PR interval prolongation or signs of GI toxicity should not be used to guide progressive dosing of digoxin. Digitalis glycosides can aggravate cellular calcium overloading and electrical instability common in failing myocardial cells. Digitalis can stimulate spontaneous automaticity of myocardial cells by inducing and potentiating late afterdepolarizations; cellular stretch, calcium overloading, and hypokalemia enhance this effect. Toxic concentrations of digitalis also enhance automaticity by increasing sympathetic tone to the heart. Furthermore, the parasympathetic effects of slowed conduction and altered refractory period facilitate development of reentrant arrhythmias. Digitalis intoxication should be suspected in patients taking the drug when ventricular arrhythmias and/or tachyarrhythmias with impaired conduction appear.

Therapy for digitalis toxicity depends on its manifestations. GI signs usually respond to drug withdrawal and correction of fluid or electrolyte abnormalities. AV conduction disturbances resolve after drug withdrawal, although sometimes anticholinergic therapy is needed. Digitalis-induced ventricular tachycardia and frequent ventricular premature complexes are generally treated with lidocaine. This drug reduces sympathetic nervous tone and can suppress arrhythmias caused by reentry and late afterdepolarizations; it has little effect on sinus rate or AV nodal conduction. If lidocaine is ineffective, phenytoin (diphenylhydantoin) is the second drug of choice in dogs; its effects are similar to those of lidocaine. IV administration of phenytoin must be slow to prevent hypotension and myocardial depression caused by the propylene glycol vehicle. Phenytoin has occasionally been used orally to treat or prevent ventricular tachyarrhythmias caused by digitalis.

Other measures are also helpful for digoxin toxicity, including IV potassium supplementation if the serum potassium concentration is <4 mEq/L (see p. 62). Magnesium supplementation may also be effective in suppressing arrhythmias; MgSO<sub>4</sub> has been used at 25 to 40 mg/kg via slow intravenous bolus, followed by infusion of the same dose over 12 to 24 hours. Fluid therapy is indicated to correct dehydration and maximize renal function. A β-blocker may help control ventricular tachyarrhythmias, but this is not used if AV conduction block is present. Quinidine should not be used because it increases the serum concentration of digitalis. Oral administration of the steroid-binding resin cholestyramine is useful only very soon after accidental overdose of digoxin because this drug undergoes minimal enterohepatic circulation. A preparation of digoxin-specific antigen-binding fragments (digoxin-immune Fab) derived from ovine antidigoxin antibodies has occasionally been used for digoxin and digitoxin overdose. The Fab fragment binds with antigenic determinants on the digoxin molecule, preventing and reversing the pharmacologic and toxic effects of digoxin. The Fab fragment-digoxin complex is subsequently excreted by the kidney. Each 38 mg vial will bind about 0.6 mg digoxin. The recommended human dose is: # vials needed = (serum digoxin concentration  $[ng/ml] \times$ body weight [kg])/100. A modified formula (Senior et al, 1991) taking the volume of distribution of digoxin in the dog into account is: # vials needed = body load of digoxin (mg)/0.6 mg of digoxin. The body load of digoxin = (serum digoxin concentration [ng/ml] /1000)  $\times$  14 L/kg  $\times$  body weight [kg].

## OTHER VASODILATORS

Vasodilators can affect arterioles, venous capacitance vessels, or both ("balanced" vasodilators). Arteriolar dilators relax arteriolar smooth muscle and thereby decrease systemic vas-

cular resistance and afterload on the heart. This facilitates ejection of blood and also can be useful in treating animals with hypertension. In patients with mitral regurgitation, arteriolar dilators decrease the systolic pressure gradient across the mitral valve, reduce regurgitant flow, and enhance forward flow into the aorta. Reduced regurgitant flow can diminish left atrial pressure, pulmonary congestion, and possibly left atrial size.

Arteriolar or mixed vasodilator therapy is generally begun with low doses to avoid hypotension and reflex tachycardia. Reduction in concurrent diuretic dosage may be advisable. Monitoring for signs of hypotension is especially important. Sequential arterial blood pressure measurement for several hours after dosage increase is preferred. A mean arterial pressure of 70 to 80 mm Hg or a venous pO<sub>2</sub> of >30 mm Hg (from a free-flowing jugular vein) is the suggested therapeutic goal for dosage titration. Systolic pressures of less than 90 to 100 mm Hg should be avoided. Clinical signs of druginduced hypotension include weakness, lethargy, tachycardia, and poor peripheral perfusion. The vasodilator dose can be titrated upward, if necessary, while monitoring for hypotension with each increase in dose.

Venodilators relax systemic veins, increase venous capacitance, decrease cardiac filling pressures (preload), and reduce pulmonary congestion. Goals of venodilator therapy are to maintain central venous pressure at 5 to 10 cm  $\rm H_2O$  and pulmonary capillary wedge pressure at 12 to 18 mm  $\rm Hg$ .

## Hydralazine

Hydralazine directly relaxes arteriolar smooth muscle when the vascular endothelium is intact, but it has little effect on the venous system. The drug reduces arterial blood pressure, improves pulmonary edema, and increases jugular venous oxygen tension (presumably from increased cardiac output) in dogs with mitral insufficiency and heart failure. The most common indication for hydralazine is acute, severe CHF from mitral regurgitation. Hydralazine has been associated with significant reflex tachycardia in some animals; the dosage should be reduced if this occurs. Hydralazine can contribute to the enhanced NH response in patients with heart failure, which makes it less desirable than ACEIs for chronic use. However, it can be useful for animals that cannot tolerate an ACEI.

Hydralazine has a faster onset of action than amlodipine. Its effect peaks within 3 hours and lasts up to 12 hours. Administration of hydralazine with food decreases bioavailability by over 60%. There is also extensive first-pass hepatic metabolism of this drug. However, in dogs increased doses saturate this mechanism and increase bioavailability. General precautions for initiating and titrating therapy are outlined in the preceding section.

Hypotension is the most common adverse effect of hydralazine therapy. GI upset also can occur, which may require drug discontinuation. High dosages have been associated with a lupuslike syndrome in people, although this has not been reported in animals.

## **Amlodipine**

This dihydropyridine L-type Ca<sup>+-</sup> channel blocker causes peripheral vasodilation as its major action, which tends to offsets any negative inotropic effect. Amlodipine has little effect on AV conduction. Besides being used to treat hypertension in cats and sometimes dogs (see Chapter 11), it is an adjunctive therapy for refractory CHF. In dogs that cannot tolerate ACEIs, amlodipine could be used in combination with a nitrate.

Amlodipine's oral bioavailability is good. It has a long duration of action (at least 24 hours in dogs). Plasma concentration peaks in 3 to 8 hours; half-life is about 30 hours. Plasma concentrations increase with long-term therapy. Maximal effect develops over 4 to 7 days after therapy is begun in dogs. The drug is metabolized in the liver. Elimination is through the urine and feces. Because of the delay in achieving maximum effect, low initial doses and weekly blood pressure monitoring during slow up-titration are recommended.

#### **Prazosin**

Prazosin selectively blocks  $\alpha_1$ -receptors in both arterial and venous walls. It is not often used for chronic CHF management because drug tolerance can develop over time and the capsule dose-size is inconvenient in small animals. In addition, controlled clinical studies in dogs are lacking. Hypotension is the most common adverse effect, especially after the first dose. Tachycardia should occur less frequently than with hydralazine because presynaptic  $\alpha_2$ -receptors, important in the feedback control of norepinephrine release, are not blocked.

## **Nitrates**

Nitrates act as venodilators. They are metabolized in vascular smooth muscle to produce NO, which indirectly mediates vasodilation. Nitroglycerin ointment or isosorbide dinitrate are used occasionally in the management of chronic CHF, either combined with standard therapy for refractory CHF or with hydralazine or amlodipine in animals that cannot tolerate ACEIs. Nitrates effect blood redistribution in people, but there are few studies involving dogs, especially using the oral route for CHF management. There is extensive first-pass hepatic metabolism, and the efficacy of oral nitrates is questionable. Nitroglycerine ointment (2%) is usually applied cutaneously (see p. 60). Self-adhesive, sustained-release preparations may be useful, but they have not been systematically evaluated in small animals. Transdermal patches, 5 mg, applied for 12 hours per day, have been used with anecdotal success in large dogs. Large doses, frequent application, or long-acting formulations are most likely to be associated with drug tolerance. Whether intermittent treatment (with drug-free intervals) will prevent nitrate tolerance from developing in dogs and cats is unknown.

#### **DIETARY CONSIDERATIONS**

Heart failure can interfere with the kidney's ability to excrete sodium and water loads. Therefore dietary sodium restriction is recommended to help control fluid accumulation and reduce necessary drug therapy. Chloride restriction also appears important. However, very low salt intake can increase rennin-angiotension system activation. It is unclear whether a reduced-salt diet is necessary before overt CHF develops, but refraining from feeding the patient high-salt table scraps or treats would appear prudent. High-salt foods include processed meats; liver and kidney; canned fish; cheese, margarine, or butter; canned vegetables; breads; potato chips, pretzels, and other processed snack foods; and dog treats such as rawhide and biscuits.

Moderate salt restriction is advised when clinical heart failure develops. This represents a sodium intake of about 30 mg/kg/day (about 0.06% sodium for canned food or 210 to 240 mg/100 g of dry food). Diets for senior animals or those with renal disease usually provide this level of salt. Prescription cardiac diets usually have greater sodium restriction (e.g., 13 mg sodium/kg/day, or about 90 to 100 mg sodium/100 g of dry food, or 0.025% sodium in a canned food) and can be helpful in patients with advanced heart failure. Severe sodium restriction (e.g., 7 mg/kg/day) can exacerbate NH activation and contribute to hyponatremia. A well-balanced diet and adequate caloric and protein intake are important. Recipes for homemade low-salt diets are available, but providing balanced vitamin and mineral content may be difficult. Drinking water in some areas can contain high sodium concentrations. Nonsoftened water or (where water from the public water supply contains more than 150 ppm of sodium), distilled water can be recommended to further decrease salt intake. Supplementation of specific nutrients is important in some cases (discussed in more detail later in this section).

Inappetence is common in dogs and cats with advanced heart failure. However, more calories may be needed because of increased cardiopulmonary energy consumption or stress. Malaise, increased respiratory effort, azotemia, digoxin toxicity, and adverse effects of other medications all can contribute to poor appetite. Meanwhile, poor splanchnic perfusion, bowel and pancreatic edema, and secondary intestinal lymphangiectasia may reduce nutrient absorption and promote protein loss. Hypoalbuminemia and reduced immune function may develop. Such factors, as well as renal or hepatic dysfunction, also can alter the pharmacokinetics of certain drugs.

Strategies that sometimes help improve appetite include warming the food to enhance its flavor, adding small amounts of very palatable human foods (e.g., nonsalted meats or gravy, low-sodium soup), using a salt substitute (KCl) or garlic powder, handfeeding, and providing small quantities of the diet several times a day. If a change in diet is indicated, a gradual switch improves acceptance (e.g., mixing the new with the old diet in a 1:3 ratio for several days, then 1:1 for several days, then 3:1, and finally the new diet alone).

Cardiac cachexia is the syndrome of muscle wasting and fat loss associated with some cases of chronic CHF. Loss of muscle over the spine and gluteal region is usually noted first. Weakness and fatigue are seen with loss of lean body mass; cardiac mass also can be affected. Cardiac cachexia is thought to be a predictor of poor survival, and it is associated with reduced immune function in people. The pathogenesis of cardiac cachexia involves multiple factors, including proinflammatory cytokines, TNF<sub>cc</sub>, and interleukin-1. These substances suppress appetite and promote hypercatabolism. Dietary supplementation with fish oils, which are high in omega-3 fatty acids (eicosapentaenoic [EPA] and docosahexaenoic [DHA] acids) can reduce cytokine production and may improve endothelial function, among other beneficial effects. Approximate doses of 27 mg/kg/day EPA and 18 mg/kg/day DHA produced improvement in cachexia and lower interleukin-1 levels in dogs with dilated cardiomyopathy, although there was no effect of fish oil on overall mortality (Freeman, 1998). Whether higher EPA and DHA doses would provide added benefit is not known; 30 to 40 mg/kg/ day EPA and 20 to 25 mg/kg/day DHA orally have been recommended.

Grossly overweight pets with heart disease may benefit from a weight-reducing diet. Obesity increases metabolic demands on the heart and expands blood volume. This could increase cardiac filling and stimulate hypertrophy, increase venous pressure, and predispose the patient to arrhythmias as well as alter cardiac metabolism. Mechanical interference with respiration promotes hypoventilation; this can contribute to cor pulmonale and complicate preexisting heart disease.

## Taurine

Taurine is an essential nutrient for cats. Prolonged deficiency causes myocardial failure as well as other abnormalities (see p. 151). Most commercial and prescription cat foods are well supplemented with taurine, which has markedly reduced the prevalence of taurine-responsive dilated cardiomyopathy in cats. But taurine concentrations should be measured in cats diagnosed with dilated cardiomyopathy, because the diet of some cats may still be deficient. Taurine-deficient cats are given oral supplements of taurine (250 to 500 mg) twice daily.

Some dogs with dilated cardiomyopathy appear deficient in taurine and/or L-carnitine, most notably American Cocker Spaniels but also others (see p. 136). Dogs fed protein-restricted diets can become taurine deficient, and some develop evidence of dilated cardiomyopathy. Taurine supplementation for dogs <25 kg is 500 to 1000 mg every 8 hours; for dogs 25 to 40 kg the dose is 1 to 2 g every 8 to 12 hours. Although not all taurine-deficient American Cocker Spaniels need both taurine and L-carnitine, most appear to.

### L-carnitine

Although L-carnitine deficiency has been identified in Boxers and Doberman Pinschers with dilated cardiomyopathy, its prevalence is thought to be low and the number of affected dogs responsive to L-carnitine supplementation even lower. Nevertheless, a trial period of supplementation (at a higher dosage) may be worthwhile. After at least 4 months, reevalu-

ation by echocardiogram is done to assess LV functional improvement. Dogs treated with carnitine supplementation may give off a peculiar odor.

The minimum effective dose of L-carnitine is not known; it may vary with the type of deficiency, if present at all. Several dose ranges have been suggested, including 50 to 100 mg/kg every 8 to 12 hours for systemic deficiency or 200 mg/kg every 8 hours for myopathic deficiency. Others use 1 g of oral L-carnitine every 8 hours for dogs <25 kg and a dose of 2 g every 12 hours for dogs between 25 and 40 kg. About ½ teaspoonful of pure L-carnitine powder is the equivalent of 1 g. Both taurine and L-carnitine can be mixed with food for easier administration.

## Other Supplements

The role of other dietary supplements is unclear. Oxidative stress and free-radical damage probably play a role in the pathogenesis of myocardial dysfunction. Cytokines such as TNF, shown to increase in the circulation in heart failure, can promote oxidative stress. In people vitamin C supplementation has a beneficial effect on endothelial function, cardiac morbidity, and mortality. But the role of supplemental antioxidant vitamins in CHF is unclear, especially in animals. Whether coenzyme Q-10 provides any measurable benefit is controversial.

## Beta-Blockers in Patients With Heart Failure

β-blockers must be used cautiously, especially in animals with myocardial failure, because of their negative inotropic effects. An important role is in the management of certain arrhythmias, such as atrial fibrillation, and some ventricular tachyarrhythmias (see Chapter 4). Another potential role for some \( \beta \)-blockers is in modulating the processes that lead to pathologic cardiac remodeling in patients with heart failure. It is well known that certain agents, in people, can improve cardiac function, reverse pathologic ventricular remodeling, and reduce mortality with chronic therapy. Carvedilol (a third-generation β-blocker) appears to be most effective in this regard, but some second-generation β-blockers (e.g., metoprolol) also show a survival benefit. It is possible that carvedilol or metoprolol might play a similar beneficial role in dogs, especially those with dilated cardiomyopathy, but the clinical efficacy of this in dogs (and cats) is presently not

Carvedilol blocks  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -adrenergic receptors but is without intrinsic sympathomimetic activity. It has antioxidant effects, reduces endothelin release, has some  $Ca^{++}$  blocking effect, and also is thought to promote vasodilation by affecting either NO or prostaglandin mechanisms. Peak plasma concentrations appear to be quite variable after oral administration. The drug is eliminated mainly through hepatic metabolism. The half-life is short (<2 hours) in dogs; an active metabolite is thought to account for the nonselective  $\beta$ -blocking effect, which lasts for 12 to 24 hours. Some experimental evidence suggests that metoprolol also may produce beneficial effects on myocardial function in dogs,

but ability to improve function and survival in clinical cases is unknown

Dogs with occult myocardial dysfunction, stable compensated CHF (e.g., no evidence of congestion for at least a week or more) caused by cardiomyopathy, or chronic mitral regurgitation that show signs of myocardial dysfunction (and compensated CHF) are likely good candidates for carvedilol (or metoprolol) therapy. There are presently no definitive guidelines. Initially, very low doses are used, along with conventional CHF therapy as indicated. β-blocker up-titration is done slowly. The dosage is increased every 1 to 2 weeks, if possible, over a 2-month period, to a target dose or as tolerated. Anecdotal experience suggests a starting dose of 0.05 to 0.1 mg/kg every 24 hours for carvedilol, with an eventual target of 0.2 to 0.3 mg/kg every 12 hours (or higher) if tolerated. An initial metoprolol dose might be 0.1 to 0.2 mg/kg/ day, with an eventual target of 1 mg/kg (if tolerated). Careful monitoring is important because CHF decompensation, bradycardia, and hypotension can occur.

## CHRONIC DIASTOLIC DYSFUNCTION

Furosemide is continued orally in patients that have developed CHF from hypertrophic cardiomyopathy and other causes of diastolic dysfunction. Gradual reduction to the lowest dosage level and frequency that are effective for controlling edema is the aim. A  $\beta$ -blocker or diltiazem has traditionally also been used, but the efficacy of this in cats with chronic CHF from hypertrophic cardiomyopathy is unclear. An ACEI in such cases is thought to be beneficial, unless it provokes hypotension, particularly in cats with dynamic LV outflow obstruction (see Chapter 8). Spironolactone can also be useful as an adjunct therapy, especially for cases with recurrent pleural effusion.

#### REEVALUATION AND MONITORING

Client education is important when managing dogs and cats with chronic heart failure. A good understanding of the pet's underlying disease, the signs of heart failure, and the purpose and potential adverse effects of each medication make early identification of complications more likely. Frequent reevaluation is important in patients with chronic heart failure because underlying diseases progress and complications often develop. The time frame for recheck visits may vary from weekly to every 6 months or so, depending on the severity of heart disease and the clinical stability of the patient.

Medications and dosage schedules should be reviewed at each visit, and problems with drug administration or signs of adverse effects ascertained. How well the animal has responded to medications, the diet and appetite level, activity level, and any other concerns should also be discussed. It is helpful to have owners monitor their pet's respiratory (and, if possible, heart) rate when the animal is asleep or resting at home. Resting respiratory rates for normal animals in the home environment are usually  $\leq 30$  breaths/minute. A persistent increase (of  $\geq 20\%$ ) in resting respiratory rate is often an early sign of worsening heart failure. This is because

pulmonary edema increases lung stiffness, which induces faster, more shallow respiration. Likewise, a persistent increase in resting heart rate accompanies the heightened sympathetic tone of decompensating failure.

A thorough physical examination, with emphasis on the cardiovascular system (see Chapter 1), is important at each evaluation. Depending on the patient's status, clinical tests might include a resting electrocardiogram (ECG) or ambulatory monitoring, thoracic radiographs, serum biochemistry analyses, an echocardiogram, serum digoxin concentration, or others. Periodic measurement of serum electrolyte and creatinine or BUN concentrations is recommended. Electrolyte imbalance (especially hypokalemia or hyperkalemia, hypomagnesemia, and sometimes hyponatremia) can occur from the use of diuretics, ACEIs, and salt restriction. Prolonged anorexia can contribute to hypokalemia, but potassium supplementation should not be used without documenting hypokalemia, especially when ACEIs and spironolactone are prescribed. Serum magnesium concentration does not accurately reflect total body stores; however, supplementation may be especially beneficial in animals that develop ventricular arrhythmias while receiving furosemide and digoxin.

Many factors can exacerbate the signs of heart failure, including physical exertion, infection, anemia, exogenous fluid administration (excess volume or sodium load), high-salt diet or dietary indiscretion, erratic administration of medication, inappropriate medication dosage for the level of disease, development of cardiac arrhythmias, environmental stress (e.g., heat, humidity, cold, smoke), development or worsening of concurrent extracardiac disease, and progression of underlying heart disease (e.g., ruptured chordae tendineae, left atrial tear, secondary right heart failure). Repeated episodes of acute, decompensated congestive failure that may require hospitalization and intensive diuresis are relatively common in patients with chronic progressive heart failure.

# STRATEGIES FOR REFRACTORY CONGESTIVE HEART FAILURE

Recurrent CHF while on initial therapy with furosemide and an ACEI is usually first handled by increasing the dose of furosemide and/or maximizing the ACEI dose. Pimobendan or digoxin, if not previously used, is added if inotropic support is indicated. Other ancillary therapy could include an additional diuretic or vasodilator. Spironolactone is recommended because of its action as an aldosterone antagonist and its likely cardioprotective effects. Because its benefits are thought to extend beyond additional diuresis, use of spironolactone earlier in the course of therapy may be advantageous. Some animals benefit from the addition of a thiazide diuretic as failure becomes more refractory.

Low doses of an arteriolar vasodilator to further reduce afterload (e.g., amlodipine or hydralazine) can further intensify therapy for dogs with CHF caused by mitral regurgitation or dilated cardiomyopathy. Blood pressure should be monitored. An arteriolar vasodilator is not recommended for cats with hypertrophic cardiomyopathy or dogs with fixed ventricular outflow obstruction (e.g., subaortic stenosis).

## Suggested Readings

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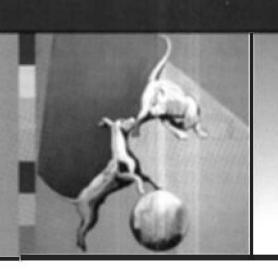
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# CHAPTER

# Cardiac Arrhythmias and Antiarrhythmic Therapy



## CHAPTER OUTLINE

#### GENERAL CONSIDERATIONS

Development of Arrhythmias

Approach to Arrhythmia Management

DIAGNOSIS AND MANAGEMENT OF COMMON

**ARRHYTHMIAS** 

Clinical Presentation

Tachyarrhythmias

Bradyarrhythmias

#### ANTIARRHYTHMIC AGENTS

Class I Antiarrhythmic Drugs

Class II Antiarrhythmic Drugs: [ -Adrenergic Blockers

class III Antiarrhythmic Drugs

Class IV Antiarrhythmic Drugs: Calcium Entry Blockers

Anticholinergic Drugs

Sympathomimetic Drugs

Other Drugs

### GENERAL CONSIDERATIONS

Cardiac arrhythmias occur for many reasons. Although some arrhythmias are of no clinical consequence, others cause serious hemodynamic compromise and sudden death, especially in animals with underlying heart disease. It is important to make an accurate electrocardiographic diagnosis, as well as to consider the arrhythmia's clinical context, before deciding whether to use antiarrhythmic therapy. In people the risk of death associated with ventricular tachyarrhythmias is higher when myocardial function is impaired. Dogs with cardiomyopathy also have increased risk for sudden death, especially Doberman Pinschers and Boxers. An inherited disorder predisposing to sudden death has also been identified in young German Shepherds. On the other hand, in previously healthy animals the ventricular premature activity that occurs commonly after thoracic trauma or splenectomy (see p. 139) is usually benign and resolves without therapy.

Occasional ventricular premature complexes occur without consequence in many animals. However, arrhythmias that compromise cardiac output and coronary perfusion can lead to myocardial ischemia, deterioration of cardiac pump function, and sometimes sudden death. These arrhythmias tend to be either very rapid (e.g., sustained ventricular or supraventricular tachyarrhythmias) or very slow (e.g., advanced atrioventricular [AV] block with a slow or unstable ventricular escape rhythm). Sometimes, however, a lethal arrhythmia such as ventricular fibrillation (VF) occurs without antecedent sustained arrhythmia. Rapid sustained tachycardia of either supraventricular or ventricular origin reduces cardiac output acutely and eventually leads to myocardial dysfunction and congestive heart failure (CHF).

### **DEVELOPMENT OF ARRHYTHMIAS**

Multiple factors underlie disturbances in cardiac rhythm. Abnormalities of conduction or automaticity caused by cardiac structural or pathophysiologic remodeling can predispose to arrhythmias, even in the absence of overt cardiac disease. Genetic factors and environmental stresses contribute to this. However, additional triggering (e.g., premature stimulus or abrupt change in heart rate) and/or modulating factors (e.g., changes in autonomic tone, circulating catecholamines, ischemia, or electrolyte disturbances) are thought to be necessary to provoke and sustain a rhythm disturbance. For example, episodes of anger or aggressive behavior have been linked to increased susceptibility to ischemic arrhythmias and sudden arrhythmic death in both dogs and people. Various stresses that lead to cardiac remodeling changes also may play a role in the development of arrhythmias. Remodeling can involve myocyte hypertrophy, changes in the structure or function of ion channels, tissue fibrosis, or the activity of the autonomic nervous system (see Chapter 3). Although some of these changes act as beneficial compensatory mechanisms in the short term, they can have harmful and arrhythmogenic long-term effects. It is thought that if such underlying arrhythmogenic modulators could be controlled, arrhythmias would be lessened. Such modulators include catecholamines, free radicals, angiotensin II, cytokines, and nitric oxide (NO). The higher survival in human patients with heart failure treated with angiotensin converting enzyme (ACE) inhibitors, spironolactone, and/or some  $\beta$ -blockers supports this approach. There is similar evidence for ACE inhibitors in dogs with dilated cardiomyopathy and reason to suspect that other therapies might be beneficial as well.

# APPROACH TO ARRHYTHMIA MANAGEMENT

If antiarrhythmic drug therapy is considered, its goals should be defined. An immediate goal is to restore hemodynamic stability. Although ideal goals include conversion to sinus rhythm, correction of underlying cause, and prevention of further arrhythmia and sudden death, suppression of all abnormal beats is generally not a realistic goal. Successful therapy may mean sufficient reduction in frequency (e.g., by ≥70-80%) or repetitive rate of ectopic beats to promote normal hemodynamics and eliminate clinical signs. However, even with apparently complete conversion to sinus rhythm, the risk of sudden death from a lethal arrhythmia may remain.

Various arrhythmias and their ECG characteristics are described in Chapter 2. This section provides a general approach to managing cardiac rhythm disturbances. Nevertheless, much remains to be learned about effective arrhythmia management and the prevention of sudden death.

- 1. Record and interpret an ECG (Box 4-1); identify and define any arrhythmia. An extended ECG recording period may be needed (e.g., Holter monitor or prolonged in-hospital monitoring).
- 2. Evaluate the whole patient, including history, physical exam findings, and clinical/laboratory test results. Are signs of hemodynamic impairment evident (e.g., episodic weakness, syncope, signs of congestive heart failure)? Are other signs of cardiac disease present (e.g., heart murmur, cardiomegaly)? Are there additional abnormalities (e.g., fever, abnormal blood chemistry values, respiratory or other extracardiac disease, trauma)? Is the animal receiving any medications? Correct what can be corrected.
- 3. Decide whether to use antiarrhythmic drug therapy. Consider signalment, history, clinical signs, and underlying disease as well as the potential benefits/risks of the drug(s) under consideration.
- If an antiarrhythmic drug is to be used, define the goals of therapy for this patient.
- 5. Initiate treatment and determine drug effectiveness. Adjust dose or try alternate agents, if needed.
- Monitor patient status. Assess arrhythmia control (consider repeated Holter monitoring), manage underlying disease(s), and watch for adverse drug effects and other complications.

# DIAGNOSIS AND MANAGEMENT OF COMMON ARRHYTHMIAS

Cardiac arrhythmias in a given animal often occur inconsistently and are influenced by drug therapy, prevailing auto-



BOX 4-1

#### **ECG Interpretation Guide**

- Determine the heart rate. Is it too fast, too slow, or normal?
- 2. Is the rhythm regular or irregular?
- Is sinus rhythm present (with or without other abnormalities), or are there no consistent P-QRS-T relationships?
- 4. Are all P waves followed by a QRS and all QRS complexes preceded by a P wave?
- 5. If premature (early) complexes are present, do they look the same as sinus QRS complexes (implying atrial or junctional [supraventricular] origin), or are they wide and of different configuration than sinus complexes (implying a ventricular origin or possibly abnormal ventricular conduction of a supraventricular complex)?
- 6. Are premature QRS complexes preceded by an abnormal P wave (suggesting atrial origin)?
- 7. Are there baseline undulations instead of clear and consistent P waves, with a rapid, irregular QRS occurrence (compatible with atrial fibrillation)?
- 8. Are there long pauses in the underlying rhythm before an abnormal complex occurs (escape beat)?
- 9. Is an intermittent AV conduction disturbance present?
- 10. Is there a lack of consistent temporal relationship between P waves and QRS complexes, with a slow and regular QRS occurrence (implying complete AV block with escape rhythm)?
- 11. For sinus and supraventricular complexes, is the mean electrical axis normal?
- 12. Are all measurements and waveform durations within normal limits?

See Chapter 2 for more specific information.

nomic tone, baroreceptor reflexes, and variations in heart rate. Treatment decisions are based on consideration of the origin (supraventricular or ventricular), timing (premature or escape), and severity of the rhythm disturbance, as well as the clinical context. Accurate ECG interpretation is important. Although a routine (resting) ECG documents arrhythmias present during the recording period, it provides only a glimpse of the cardiac rhythms occurring over time. Because marked variation in frequency and severity of arrhythmias may occur over time, potentially critical arrhythmias are easily missed. For this reason, Holter monitoring or other forms of extended ECG acquisition are useful in assessing the severity and frequency of arrhythmias and monitoring treatment efficacy. Some rhythm abnormalities do not require therapy, whereas others demand immediate aggressive treatment. Close patient monitoring is especially important in patients with more serious arrhythmias.

Supraventricular tachyarrhythmias occur from various mechanisms, including reentry involving the AV node, accessory pathways, or sinoatrial (SA) node, as well as abnormal automaticity within atrial or junctional tissue. Many patients have atrial enlargement. Common underlying heart diseases



BOX 4-2

### Factors Predisposing to Arrhythmias

## Atrial Arrhythmias

#### Cardiac

Mitral or tricuspid insufficiency Dilated cardiomyopathy Hypertrophic cardiomyopathy Restrictive cardiomyopathy

Cardiac neoplasia

Congenital malformation
Accessory AV nodal bypass tract(s)

Myocardial fibrosis High sympathetic tone

İschemia

Intractrial catheter placement

#### Extracardiac

Catecholamines Electrolyte imbalances Digoxin toxicity

Other drugs (anesthetic agents, bronchodilators)

Acidosis/alkalosis

Hypoxia Thyrotoxicosis Severe anemia Electric shock Thoracic surgery

## Ventricular Arrhythmias

#### Cardiac

Congestive heart failure

Cardiomyopathy (especially Doberman Pinschers and

Boxers) Myocarditis Pericarditis Degenerative valvular disease with myocardial fibrosis

Ischemia

Trauma

Cardiac neoplasia Heartworm disease Congenital heart disease

Ventricular dilation

Mechanical stimulation (intracardiac catheter, pacing wire)

#### Extracardiac

Hypoxia

Electrolyte imbalances (especially K\*)

Acidosis/alkalosis Thyrotoxicosis Hypothermia Fever

Sepsis/toxemia

Trauma (thoracic or abdominal)

Gastric dilation/volvulus Splenic mass or splenectomy

Hemangiosarcoma Pulmonary disease

Uremia Pancreatitis Pheochromocytoma

Other endocrine diseases (diabetes mellitus, Addison's

disease, hypothyroidism)

High sympathetic tone (pain, anxiety, fever)

Central nervous system disease (increases in sympathetic or vagal stimulation)

Electric shock

Drugs (digoxin, sympathomimetics, anesthetics, tranquilizers, anticholinergics, antiarrhythmics)

include chronic mitral or tricuspid valve degeneration with regurgitation, dilated cardiomyopathy, congenital malformations, and cardiac neoplasia. Other factors also may predispose to atrial tachyarrhythmias (Box 4-2).

Ventricular premature contractions (VPCs) occur in association with disorders that affect cardiac tissue directly or indirectly through neurohormonal effects (see Box 4-2). For instance, disorders of the central nervous system can produce abnormal neural effects on the heart that cause ventricular or supraventricular arrhythmias (brain-heart syndrome). When VPCs are infrequent or underlying cardiac function is normal, adverse hemodynamic effects may be negligible. However, hemodynamic impairment can be severe in dogs or cats with underlying heart disease, rapid ventricular rates, or myocardial depression stemming from a systemic disease.

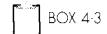
Factors such as underlying hypoxia, electrolyte or acidbase imbalances, and abnormal hormone concentrations (e.g., thyroid) can exacerbate arrhythmias. Therefore corfecting these is usually important for arrhythmia control. Because some drugs can provoke arrhythmias, reducing dosage or discontinuing the medication may be useful.

## **CLINICAL PRESENTATION**

Box 4-3 lists common arrhythmias according to a clinical description of the heartbeat.

# TACHYARRHYTNMIAS Rapid Irregular Rhythms

Irregular heart rhythms are common, and the ECG is important for differentiating abnormal rhythms as well as sinus arrhythmia. Pulse deficits (see p. 6) and an irregular, weak pulse with heart sounds of varying intensity and regularity may be detected on physical examination. Premature contractions interrupt ventricular filling and reduce stroke volume, sometimes to the extent that there is no ejection at all for that cycle (Fig. 4-1). Rapid atrial fibrillation (AF) and premature contractions of any origin often cause pulse deficits. Ventricular premature complexes can cause audible splitting of the heart sounds because of asynchronous ven-



Clinical Characterization of Common Heart Rate and Rhythm Disturbances

#### Fast, Irregular Rhythms

Atrial or supraventricular premature contractions Paroxysmal atrial or supraventricular tachycardia Atrial flutter or fibrillation Ventricular premature contractions Paroxysmal ventricular tachycardia

#### Fast, Regular Rhythms

Sinus tachycardia Sustained supraventricular tachycardia Sustained ventricular tachycardia

### Slow, Irregular Rhythms

Sinus bradyarrhythmia Sinus arrest Sick sinus syndrome High-grade 2<sup>nd</sup> degree AV block

#### Slow, Regular Rhythms

Sinus bradycardia
Complete (third-degree) AV block with ventricular escape
rhythm
Atrial standstill with ventricular escape rhythm

tricular activation. Ventricular and supraventricular tachycardias and AF cause more severe hemodynamic compromise than do isolated premature contractions, especially in patients with underlying heart disease.

### Rapid Regular Rhythms

Rapid regular rhythms include sinus tachycardia, sustained supraventricular tachycardia (SVT), and sustained ventricular tachycardia. Sinus tachycardia is caused by high sympathetic tone or drug-induced vagal blockade. Underlying causes include anxiety, pain, fever, thyrotoxicosis, heart failure, hypotension, shock, the ingestion of stimulants or toxins (e.g., chocolate, caffeine), or drugs (e.g., catecholamines, anticholinergics, theophylline, and related agents). The heart rate in dogs and cats with sinus tachycardia is usually <300 beats/min, although it can be higher in those with thyrotoxicosis or in those that have ingested exogenous stimulants or drugs (particularly cats). Alleviation of the underlying cause and intravenous (IV) administration of fluids to reverse hypotension (in animals without edema) should cause the sympathetic tone and sinus rate to decrease.

SVT of varying causes can be difficult to differentiate from sinus tachycardia. The heart rate in patients with SVT is often >300 beats/min, but it is rare for the sinus rate to be this rapid. Patients with SVTs, such as sinus tachycardia, usually have a normal QRS configuration (narrow and upright in lead II). However, if an intraventricular conduc-

tion disturbance is present, SVT may resemble ventricular tachycardia. A vagal maneuver can be useful in differentiating among narrow QRS complex tachycardias.

Sustained, rapid arrhythmias lead to decrease in cardiac output, arterial blood pressure, and coronary perfusion. CHF eventually may result. Signs of poor cardiac output and hypotension include weakness, depression, pallor, prolonged capillary refill time, exercise intolerance, syncope, dyspnea, prerenal azotemia, worsening rhythm disturbances, and sometimes altered mentation, seizure activity, and sudden death.

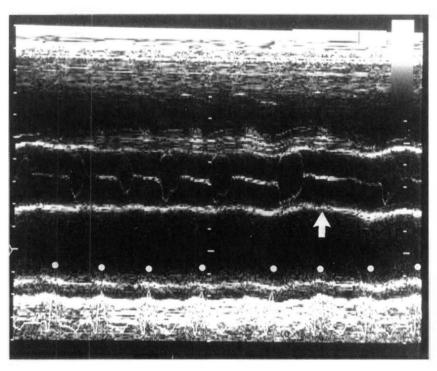
## Supraventricular Tachyarrhythmias

Occasional premature beats do not require specific therapy. Factors that predispose to these arrhythmias should be minimized as much as possible (e.g., discontinue or reduce dosage of suspected drugs, manage heart failure if present, and treat metabolic or endocrine abnormalities).

Oral therapy for frequent supraventricular premature beats and paroxysmal tachycardia. Initial oral therapy for frequent atrial premature complexes (APCs) or paroxysmal SVT usually involves either digoxin, diltiazem, a β-blocker, or a combination of these. Digoxin (see Table 3-3) is the initial oral drug of choice in dogs with heart failure and cats with dilated cardiomyopathy (Fig. 4-2). A β-blocker or the calcium entry blocker diltiazem may be added to the regimen if the arrhythmia is not controlled with digoxin, along with other therapy (including an ACE inhibitor) indicated for heart failure. Cats with hypertrophic cardiomyopathy or hyperthyroidism are usually treated with a β-blocker such as atenolol, although diltiazem is an alternative. Refractory intermittent supraventricular tachyarrhythmias may respond to amiodarone, sotalol, procainamide, quinidine, or a class IC agent.

### Acute therapy for supraventricular tachycardia.

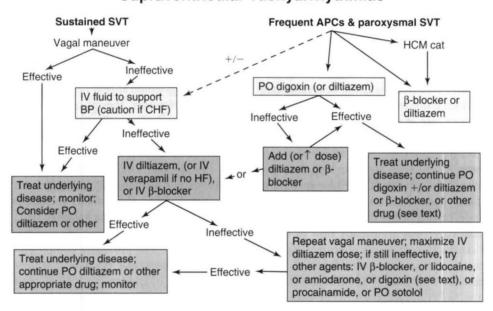
More aggressive therapy is warranted for rapid and persistent supraventricular tachyarrhythmias, especially in the face of hemodynamic impairment. A vagal maneuver can be tried first (discussed in more detail in the following section). IV access is secured, and fluids are administered to maintain blood pressure and enhance endogenous vagal tone. However, patients with known or suspected heart failure should receive a small volume slowly, if at all. If a vagal maneuver does not terminate the arrhythmia, diltiazem IV (or oral loading) is often chosen first because of its lesser negative inotropic effects. Although verapamil (IV) is equally effective against SVTs, it is not recommended for dogs with myocardial dysfunction or heart failure because of its greater negative inotropic effects. A slowly administered IV β-blocker (e.g., propranolol, esmolol) is an alternative therapy but also has negative inotropic effects in animals with high underlying sympathetic tone. Some cases of reentrant SVT or automatic atrial tachycardia respond to IV lidocaine. IV digoxin also may be tried, but this has been less effective than the calcium channel blockers. Digoxin has a slower onset of action, and although it increases vagal tone, IV administration can also increase central sympathetic output. IV amiodarone is an



#### FIG 4-1

M-mode echocardiogram at the aortic root level in a Doberman Pinscher with atrial fibrillation and dilated cardiomyopathy. Pulse deficits and variable-intensity pulses occurred secondary to the variable (or absent) aortic valve opening caused by the arrhythmia and illustrated in this echocardiogram. The motion of two aortic valve leaflets is seen within the parallel aortic root echocardiograms. Most cycles are associated with variable and poor stroke volume and with abbreviated aortic valve opening, but there is no opening at all after the sixth electrocardiogram complex from the left (arrow). R waves are indicated by white dots.

## Supraventricular Tachyarrhythmias



#### FIG 4-2

A therapeutic approach to supraventricular tachyarrhythmias. See Table 4-2 for drug doses and text for more information. APCs, Atrial premature contractions; BP, blood pressure; CHF, congestive heart failure; HCM, hypertrophic cardiomyopathy; HF, heart failure or myocardial dysfunction; SVT, supraventricular tachycardia.

alternative agent in refractory cases. Sotalol or a class IA or IC drug might be tried if the arrhythmia is unremitting. Adenosine appears to be ineffective in dogs for terminating SVTs. Further cardiac diagnostic tests are indicated once conversion is achieved or the ventricular rate has decreased to <200 beats/min. Once the rhythm is better controlled, oral diltiazem, digoxin, amiodarone, or  $\beta$ -blockers are options for chronic therapy; combinations of these agents can be used.

Paroxysmal AV reciprocating tachycardia is a reentrant tachycardia involving an accessory pathway and the AV node (see p. 27). It is interrupted by slowing conduction or prolonging the refractory period of either or both tissues. A vagal maneuver may slow AV conduction enough to terminate the rhythm. Diltiazem and β-blockers slow AV conduction and increase refractoriness. Another approach is IV amiodarone or procainamide. Digoxin slows AV conduction but has variable effects on the accessory pathway; its use is usually discouraged in people with preexcitation syndromes. Procainamide and quinidine may prevent AV reciprocating tachycardia because they lengthen the refractory period of the accessory pathway. High-dose procainamide, with or without a β-blocker or diltiazem, has been successful in preventing the recurrence of tachycardia in some cases. Intracardiac electrophysiologic mapping with radiofrequency catheter ablation of accessory pathways has been used successfully to abolish refractory SVT associated with preexcitation in dogs, although this technique is not widely available yet.

Atrial tachycardia caused by a persistent automatic ectopic focus may be particularly difficult to suppress. When the antiarrhythmic strategies outlined in the preceding paragraphs are unsuccessful, the goal of therapy shifts to ventricular rate control. By prolonging AV conduction time and refractoriness, fewer atrial impulses are then conducted and ventricular rate is slowed (and usually irregular). Therapy with combinations of diltiazem or a  $\beta$ -blocker and digoxin, sotalol, or amiodarone can be effective. The animal with persistent automatic atrial tachycardia could be a candidate for intracardiac electrophysiologic mapping and catheter ablation when such tools are available. Alternatively, heart rate control could be achieved by AV node ablation with permanent pacemaker implantation.

**Vogal maneuver.** A vagal maneuver can help the clinician differentiate among tachycardias caused by an ectopic automatic focus, those dependent on a reentrant circuit involving the AV node, or excessively rapid sinus node activation. The vagal maneuver may transiently slow or intermittently block AV conduction, exposing abnormal atrial P' waves, and allow an ectopic atrial focus to be identified. Vagal maneuvers can terminate reentrant SVTs involving the AV node by interrupting the reentrant circuit. The maneuver tends to temporarily slow the rate of sinus tachycardia.

Vagal maneuvers are performed by massaging the area over the carotid sinuses (below the mandible in the jugular furrows) or by applying firm bilateral ocular pressure for 15 to 20 seconds. Although initial attempts are often unsuccessful, repeating the vagal maneuver after antiarrhythmic drug injection may be useful.  $\beta$ -blockers, Ca<sup>+-</sup> entry-blockers, digoxin, and other agents can increase the effectiveness of vagal maneuvers. The vagal maneuver can be further potentiated in dogs by administering intramuscular (IM) morphine sulfate (0.2 mg/kg) or IV edrophonium chloride (1 to 4 mg; atropine and an endotracheal tube should be readily available).

## Ventricular Tachyarrhythmias

Occasional VPCs in an otherwise asymptomatic animal should not be treated. Moderately frequent single VPCs of uniform configuration may not require antiarrhythmic drug treatment either, especially if underlying heart function is normal. Nevertheless, guidelines as to whether, when, and how best to treat intermittent ventricular tachyarrhythmias remain undefined. Besides being expensive, antiarrhythmic drugs can have serious adverse effects, can provoke additional arrhythmias (proarrhythmic effects), and may not be efficacious. Pretreatment and posttreatment 24- to 48-hour ambulatory ECG recordings showing at least a 70% to 80% reduction in arrhythmia frequency provide the best indicator of drug arrhythmia-suppression efficacy. Intermittent ECG recordings cannot truly differentiate between drug effect (or lack thereof) and the spontaneous, marked variability of arrhythmia frequency that occurs in any individual. However, in-hospital ECG recordings of 15 seconds to several minutes in duration are often the most practical attempt to monitor arrhythmias.

Several factors influence the decision to use ventricular antiarrhythmic drug therapy. These factors include the nature of the animal's underlying disease, the perceived severity of the arrhythmia, and the presence or absence of hemodynamic compromise. Diseases such as dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy in Boxers, hypertrophic cardiomyopathy, and subaortic stenosis, among others, are frequently associated with sudden death from arrhythmias. Therefore ventricular antiarrhythmic therapy would appear most urgent in animals with these diseases. However, the efficacy of a particular therapy to prolong survival as well as suppress the arrhythmia is difficult to accurately assess. Traditional guidelines for instituting ventricular antiarrhythmic therapy have been based on frequency, prematurity, and variability of the QRS configuration of the arrhythmia. Characteristics thought to imply increased electrical instability include rapid paroxysmal or sustained ventricular tachycardia (e.g., >130 beats/min), multiform (polymorphic) VPC configuration, or close coupling of VPCs to preceding complexes (R-on-T phenomenon). However, clear evidence that these guidelines predict greater risk of sudden death in all patients is lacking. It is probably more important to consider the animal's underlying heart disease and whether the arrhythmia is causing signs of hypotension or low cardiac output. Animals that are hemodynamically unstable or have a disease associated with sudden cardiac death are treated earlier and more aggressively.

Acute therapy for ventricular tachycardia. Sustained ventricular tachycardia is treated aggressively because it can result in marked decreases in arterial blood pressure, especially at faster rates. Lidocaine (IV) is usually the first-choice drug for controlling serious ventricular tachyarrhythmias in hospitalized dogs. It is effective against arrhythmias of several underlying mechanisms and has minimal adverse hemodynamic effects. Because the effects of IV boluses last only about 10 to 15 minutes, a constant rate infusion (CRI) is warranted if the drug is effective. Small supplemental IV boluses can be given in addition to the CRI to maintain therapeutic drug concentrations until a steady state is achieved. IV infusion can be continued for several days, if needed. If lidocaine is ineffective after maximal recommended doses, several other strategies can be tried (Fig. 4-3).

IV amiodarone or oral mexiletine or sotalol can be more effective in some cases. With IV amiodarone, slow injection of conservative doses and blood pressure monitoring are recommended because marked hypotension can occur. Alternatively, procainamide (given intravenously, intramuscularly, or orally) or quinidine (given intramuscularly or orally) can be tried next. Effects of a single IM or oral loading dose of either drug should occur within 2 hours. If this is effective, lower doses can be given every 4 to 6 hours intramuscularly or orally. If ineffective, the dose can be increased or another antiarrhythmic drug chosen. Quinidine is not given intravenously because of its hypotensive effects. This drug is also not recommended in patients on digoxin or that have prolonged QT intervals. If the arrhythmia has not been controlled, a β-blocker can be added.

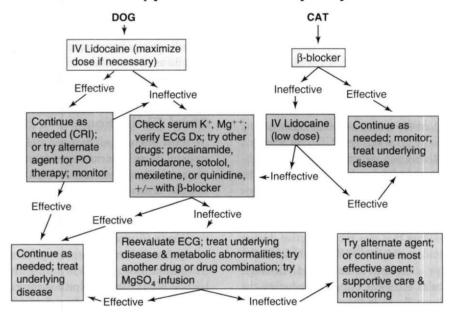
Cats with frequent ventricular tachyarrhythmias are usually given a  $\beta$ -blocker first. Alternatively, low doses of lidocaine can be administered. However, cats, especially if not anesthetized, can be quite sensitive to the neurotoxic effects of this drug. Procainamide or sotalol can also be used.

Digoxin is not used specifically for treating ventricular tachyarrhythmias, although it may be indicated for patients with concurrent heart failure and supraventricular arrhythmias. Digoxin can also predispose to the development of ventricular arrhythmias. Another antiarrhythmic drug may be necessary in animals with preexisting frequent or repetitive VPCs. Phenytoin is used only in dogs for digitalis-induced ventricular tachyarrhythmias that are refractory to lidocaine. Ancillary KCl supplementation (if serum  $K^+ \leq 4~mEq/L$ ) with or without MgSO $_4$  can increase antiarrhythmic efficacy.

Close ECG monitoring and further diagnostic testing should follow initial therapy. Total suppression of persistent ventricular tachyarrhythmias is not expected. The patient's clinical status, the underlying disease(s), the success of the drug in suppressing the arrhythmia, and the drug dosage (e.g., whether it could be increased) all influence the decision whether to continue or discontinue current treatment or to use a different drug. Clinical status and results of diagnostic testing also guide decisions about chronic oral therapy.

If the ventricular tachyarrhythmia appears refractory to initial treatment attempts, one or more of the following considerations may be helpful:

## Acute Therapy - Ventricular Tachyarrhythmias



**FIG 4-3** A therapeutic approach to ventricular tachyarrhythmias. See Table 4-2 for drug doses and text for more information. *CRI*, Constant-rate infusion; *Dx*, diagnosis; *ECG*, electrocardiogram.

- Reevaluate the ECG—could the rhythm have been incorrectly diagnosed initially? For example, SVT with an intraventricular conduction disturbance can mimic ventricular tachycardia. In such cases, IV diltiazem is usually more effective than lidocaine.
- 2. Reevaluate the serum K<sup>+</sup> (and Mg<sup>++</sup>) concentration. Hypokalemia reduces the efficacy of class I antiarrhythmic drugs (e.g., lidocaine, procainamide, quinidine) and can predispose to the development of arrhythmias. If the serum K<sup>+</sup> concentration is <3 mEq/L, KCl can be infused at 0.5 mEq/kg/hr; for serum K<sup>+</sup> between 3 to 3.5 mEq/L, KCl can be infused at 0.25 mEq/kg/hr. A serum K<sup>+</sup> concentration in the high normal range is the goal. If the serum Mg<sup>++</sup> concentration is <1.0 mg/dl, MgSO<sub>4</sub> or MgCl<sub>2</sub>, diluted in D<sub>5</sub>W, can be administered at 0.75 to 1.0 mEq/kg/day by CRI.
- 3. Maximize the dose of the conventional antiarrhythmic drug having the greatest effect.
- 4. Try amiodarone (IV), sotalol (oral), or a β-blocker in conjunction with a class I drug (e.g., propranolol, esmolol, or atenolol with procainamide or lidocaine) or a class IA drug with a IB drug (e.g., procainamide with lidocaine or mexiletine).
- 5. Consider the possibility that the drug therapy is exacerbating the rhythm disturbance (a proarrhythmic effect). Polymorphous ventricular tachycardia (torsades de pointes) has been associated with quinidine, procainamide, and other drug toxicities.
- 6. MgSO<sub>4</sub> may be effective in animals with ventricular tachyarrhythmias associated with digoxin toxicity or with suspected polymorphous ventricular tachycardia (torsades de pointes). A slowly administered IV bolus of 25 to 40 mg/kg, diluted in D₅W, followed by an infusion of the same dose over 12 to 24 hours, has been suggested. Given that MgSO<sub>4</sub> contains 8.13 mEq magnesium per gram, a similar magnesium dose is provided by calculating 0.15 to 0.3 mEq/kg.
- 7. If the animal is tolerating the arrhythmia well, continue supportive care, correct other abnormalities as possible, and continue cardiovascular monitoring alone or with the most effective antiarrhythmic drug.
- 8. Direct current (DC) cardioversion or ventricular pacing may be available at a referral center; ECG-synchronized equipment and anesthesia or sedation are required. High-energy, nonsynchronized shock (defibrillation) can be used for rapid polymorphic ventricular tachycardia or flutter degenerating into fibrillation.

Chronic oral therapy for ventricular tachyarrhythmias. The same drug that was most effective during acute therapy, or a similar one, is often continued orally when long-term therapy is thought to be needed. Although suppression of ventricular ectopy is one aim, reducing the risk of sudden arrhythmic death is the real issue for longterm therapy. Whereas the Class IB drugs (lidocaine and mexiletine) appear to raise the fibrillation threshold more than the Class IA agents (procainamide and quinidine), Class III agents appear to have much greater antifibrillatory effects than the Class I drugs. Concurrent disease should be treated if possible. It is likely that animals with arrhythmias associated with underlying heart disease also benefit from the use of  $\beta$ -blockers, ACE inhibitors, and some other therapies, as do people. However,  $\beta$ -blockers alone do not appear effective in suppressing ventricular tachyarrhythmias in Doberman Pinschers with cardiomyopathy.

Several strategies are available for long-term oral therapy of patients with ventricular tachyarrhythmias:

- A Class I agent alone: sustained-release procainamide, mexiletine, (or possibly tocainide); occasionally a class IA and IB drug are used together. However, Class I drugs provide questionable protection from VF.
- 2. A Class I agent combined with a β-blocker (Class II) agent: sustained release procainamide or mexiletine and atenolol or propranolol. β-Blockers can be useful for both ventricular and supraventricular arrhythmias that are provoked by sympathetic stimulation or release of catecholamines. β-Blockers may confer some protection against VF.
- A Class III agent: sotalol or amiodarone. These drugs may provide greater antifibrillatory protection, but they also have potentially serious adverse effects.

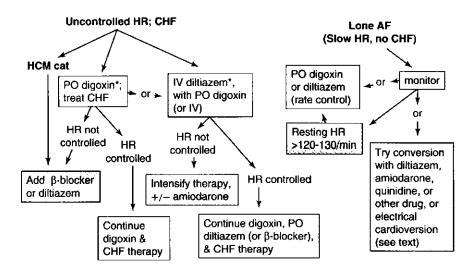
Presently, the three most favored options are sotalol; amiodarone; or mexiletine or sustained-release procainamide with atenolol, because they are likely to provide a greater antifibrillatory effect.

Frequent reevaluation is important for patients on long-term antiarrhythmic therapy (for any rhythm disturbance). Patients' owners can be shown how to use a stethoscope or palpate the chest wall to count the number of "skipped" beats per minute at home; this may yield an approximation of the frequency of arrhythmic events (either single or paroxysms). However, continuous 24- to 48-hour ambulatory ECG recordings are more accurate. The decision to continue or discontinue successful antiarrhythmic therapy is also based on consideration of the clinical situation and any underlying cardiac disease.

#### Atrial Fibrillation

AF most often develops when there is marked atrial enlargement. It is a serious arrhythmia, especially when the ventricular response rate is high. Predisposing conditions include dilated cardiomyopathy, chronic degenerative AV valve disease, congenital malformations that cause atrial enlargement, and hypertrophic or restrictive cardiomyopathy in cats. Clinical heart failure is common in these animals. AF is characterized by an irregular and usually rapid ventricular response rate. When little time is available for ventricular filling, stroke volume is compromised. Furthermore, atrial contraction (the "atrial kick"), which is especially important to ventricular filling at faster heart rates, is lost. Cardiac output tends to decrease considerably when AF develops; poor myocardial function exacerbates this decrease.

## **Atrial Fibrillation**



<sup>\*</sup> See text for precautions in animals with pre-excitation that develop AF

**FIG 4-4**A therapeutic approach to atrial fibrillation. See Table 4-2 for drug doses and text for more information. *AF*, atrial fibrillation; *CHF*, congestive heart failure; *HCM*, hypertrophic cardiomyopathy; *HR*, heart rate.

Long-lasting conversion to sinus rhythm is rare in the face of marked underlying cardiac disease, even after successful electrical cardioversion. Therefore treatment in most cases is directed at reducing the ventricular response rate by slowing AV conduction (Fig. 4-4). A slower heart rate allows more time for ventricular filling and lessens the relative importance of atrial contraction. In-hospital heart rates <150 (or 180 in cats) beats/min are desirable. Heart rate should be documented by ECG; counting the ventricular rate by auscultation or palpation is often highly inaccurate. Resting heart rate at home, which can be monitored by the owner, is a better indicator of drug effectiveness. Heart rates of 70 to 120 beats/min in dogs and 80 to 140 beats/min in cats are probably acceptable.

Therapy for atrial fibrillation. The oral drug of first choice for most dogs with AF is digoxin (see Table 3-3). If the heart rate exceeds 200 to 220 beats/min at rest, twice the eventual oral maintenance dosage can be given for 1 to 2 days. When more immediate heart rate reduction is indicated, IV diltiazem is recommended. This has less negative inotropic effect than verapamil or an IV  $\beta$ -blocker, although esmolol could be cautiously tried because of its short half-life. If dobutamine or dopamine infusion is needed to support myocardial function (see p. 60 and Box 3-1), IV diltiazem or an IV loading dose of digoxin (cautiously) can be used, but a  $\beta$ -blocker should be avoided.

Digoxin alone does not adequately reduce the heart rate in many animals. Increases in sympathetic tone from CHF, exercise, or excitement can override the vagal effect of digoxin on AV conduction. Either a  $\beta$ -blocker or diltiazem can be added and titrated upward as needed to further slow AV

conduction and ventricular rate. Because of their potential to depress myocardial function, the agent chosen is usually added 1 to 2 days after starting oral digoxin in most patients with reduced myocardial contractility. Amiodarone can be added (or substituted) for additional rate control. An occasional dog will revert to sinus rhythm in response to diltiazem or amiodarone therapy. Digoxin is not used in cats with hypertrophic cardiomyopathy that develop AF; a β-blocker or diltiazem is used instead.

When AF develops in patients that also have ventricular preexcitation, AV nodal blocking drugs ( $Ca^{++}$  blockers, digoxin, and possibly  $\beta$ -blockers) should not be used because they can paradoxically increase the ventricular response rate. Amiodarone is recommended in these cases. Sotalol or procainamide can also be used.

Electrical cardioversion of AF has been of limited success in animals; most revert to AF. Newer methods, including biphasic current delivery combined with amiodarone (or other drug) therapy, may be more successful. Nevertheless, experience with AF in people suggests that heart rate control provides similar survival benefit (and fewer adverse effects) than conversion to sinus rhythm.

## Lone atrial fibrillation

AF sometimes develops in large or giant-breed dogs without cardiomegaly or other evidence of structural heart disease. This can occur transiently, usually in association with trauma or surgery. AF with a slow ventricular response rate can also be an incidental finding in such dogs. This is known as "lone AF". Acute AF without signs of heart disease or failure may convert to sinus rhythm spontaneously or in response to

drug therapy, such as with diltiazem (e.g. PO for ~3 days), amiodarone, or possibly sotalol or other Class III or IC agents. Acute onset AF associated with high vagal tone may convert with IV lidocaine. Quinidine PO or IM has been used for acute AF conversion in large dogs without signs of heart disease; but adverse effects can include increased ventricular response rate from the drug's vagolytic effects, ataxia, and most seriously, seizures or polymorphic ventricular tachycardia. If effective, the drug is discontinued after sinus rhythm is achieved. Dogs that do not convert to sinus rhythm are either given digoxin or continued on diltiazem for rate control. Alternatively, if the ventricular rate is consistently low at rest, dogs can be monitored periodically without therapy; but rapid heart rates still are likely with exercise or excitement.

# BRADYARRHYTHMIAS Sinus Bradycardia

Slow sinus rhythm (or arrhythmia) can be a normal finding, especially in athletic dogs. Sinus bradycardia has also been associated with the administration of various drugs (e.g., xylazine, thorazine tranquilizers, some anesthetic agents, medetomidine, digoxin, calcium entry blockers,  $\beta$ -blockers, parasympathomimetic drugs), trauma or diseases of the central nervous system, organic disease of the sinus node, hypothermia, hyperkalemia, and hypothyroidism, among other disorders. Conditions that increase vagal tone (e.g., respiratory or gastrointestinal tract disease or a mass involving the vagosympathetic trunk) may induce sinus bradycardia. Chronic pulmonary disease often is associated with pronounced respiratory sinus arrhythmia.

In most cases of sinus bradycardia, the heart rate increases in response to exercise or atropine administration, and no clinical signs are associated with the slow heart rate. Symptomatic dogs usually have a heart rate slower than 50 beats/min and/or pronounced underlying disease. Because sinus bradycardia and sinus bradyarrhythmia are extremely rare in cats, a search for underlying cardiac or systemic disease (e.g., hyperkalemia) is warranted in any cat with a slow heart rate.

When sinus bradycardia is associated with signs of weakness, exercise intolerance, syncope, or worsening underlying disease, an anticholinergic (or adrenergic) agent is given (Fig. 4-5). If sinus bradycardia is the result of a drug effect, discontinuation, dosage reduction, or other therapy should be used, as appropriate (e.g., reversal of anesthesia or medetomidine, calcium salts for calcium entry blocker overdose, dopamine or atropine for  $\beta$ -blocker toxicity). If there is inadequate increase in heart rate with medical therapy, temporary or permanent pacing is indicated (see Suggested Readings).

# **Sick Sinus Syndrome**

Sick sinus syndrome is a condition of erratic sinoatrial function characterized by episodic weakness, syncope, and Stokes-Adams seizures. Older female Miniature Schnauzers and West Highland White Terriers are commonly affected in

# Symptomatic Bradyarrhythmia

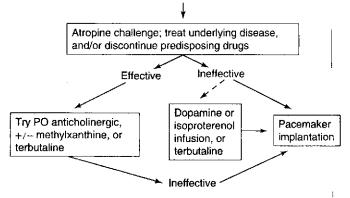


FIG 4-5
A therapeutic approach to managing symptomatic bradyar-rhythmias. See Box 3-1 and Table 4-2 and text for more information.

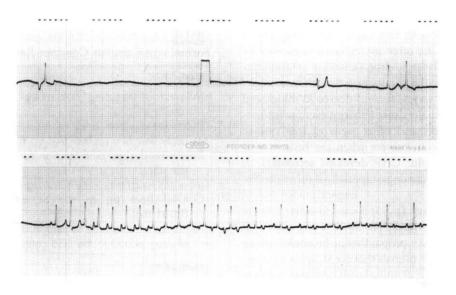
different regions, but the syndrome is also seen in Dachshunds, Cocker Spaniels, Pugs, and mixed-breed dogs. Affected dogs have episodes of marked sinus bradycardia with sinus arrest (or sinoatrial block). Sick sinus syndrome is extremely rare in cats.

Abnormalities of the AV conduction system may coexist, causing the activity of subsidiary pacemakers to be depressed and leading to prolonged periods of asystole. Some affected dogs also have paroxysmal SVTs, prompting the name *bradycardia-tachycardia syndrome* (Fig. 4-6). Premature complexes may be followed by long pauses before sinus node activity resumes, indicating a prolonged sinus node recovery time. Intermittent periods of accelerated junctional rhythms and variable junctional or ventricular escape rhythms may also occur.

Clinical signs can result from bradycardia and sinus arrest, paroxysmal tachycardia, or both. Signs can mimic seizures stemming from neurologic or metabolic disorders. Concurrent degenerative AV valve disease is also often present. Some dogs have evidence of CHF, usually secondary to AV valve regurgitation, although the arrhythmias may be a complicating factor.

ECG abnormalities are frequently pronounced in dogs with long-standing sick sinus syndrome. Nevertheless, some dogs have one or more normal resting ECGs. Prolonged visual ECG monitoring or 24-hour ambulatory ECG can help establish a definitive diagnosis. An atropine challenge test is done in dogs with persistent bradycardia (see p. 93). The normal response is an increase in the heart rate of 150% or to >130 to 150 beats/min. Dogs with sick sinus syndrome generally have a subnormal response.

Therapy with an anticholinergic agent, methylxanthine bronchodilator, or terbutaline given orally may temporarily help some animals that have a positive response to atropine challenge. However, anticholinergic or sympathomimetic drugs used to accelerate the sinus rate can also exacerbate tachyarrhythmias. Conversely, drugs used to suppress these supraventricular tachyarrhythmias can magnify the brady-



#### FIG 4-6

Continuous electrocardiogram from an 11-year-old female Miniature Schnauzer with sick sinus syndrome, illustrating a combination of bradycardia and tachycardia. The top portion shows persistent sinus arrest with three different escape complexes, followed by an atrial premature complex. There is a 1-mV calibration mark in the middle of the top strip. The bradycardia is interrupted by a run of atrial tachycardia at a rate of 250 beats/min, with 1:1 atrioventricular conduction initially; but starting in the middle of the bottom strip, every other P' wave is blocked (2:1 atrioventricular conduction).

cardia, although digoxin or diltiazem is helpful in some dogs if used cautiously. Sick sinus syndrome with frequent or severe clinical signs is best managed by permanent artificial pacing. The Suggested Readings list includes sources of further details on pacing. Dogs that remain symptomatic because of paroxysmal SVTs can safely be given appropriate antiarrhythmic therapy once a normally functioning pacemaker is in place.

# **Atrial Standstill**

Persistent atrial standstill is a rhythm disturbance characterized by lack of effective atrial electrical activity (i.e., no P waves and a flat baseline) in which a junctional or ventricular escape rhythm controls the heart. This bradyarrhythmia is rare in dogs and extremely rare in cats; most cases have occurred in English Springer Spaniels with muscular dystrophy of the fascioscapulohumeral type, although infiltrative and inflammatory diseases of the atrial myocardium can also result in atrial standstill. Because organic disease of the atrial myocardium may also involve the ventricular myocardium, persistent atrial standstill may be a harbinger of a serious and progressive cardiac disorder.

Medical treatment for persistent atrial standstill is rarely rewarding; however, an anticholinergic drug or an infusion of dopamine or isoproterenol can sometimes temporarily accelerate the escape rhythm. If ventricular tachyarrhythmias result from this treatment, the drug should be discontinued or the dose reduced. Oral terbutaline may also have some beneficial effect. Antiarrhythmic agents are contraindicated in these animals because they may suppress the

escape focus, as well as the tachyarrhythmia. Permanent pacemaker implantation is the treatment of choice, although the prognosis is poor in dogs with concurrent ventricular myocardial dysfunction.

Hyperkalemia should be ruled out in animals without P waves. The apparent lack of atrial electrical and mechanical activity ("silent atrium") caused by hyperkalemia will resolve with treatment. Sinus node activity (and P waves) become evident as the serum K<sup>+</sup> concentration returns to normal.

# **Atrioventricular Conduction Block**

Second-degree, or intermittent, AV block usually causes an irregular heartbeat. In contrast, the ventricular escape rhythm that occurs with a third-degree, or complete, AV block is regular, although premature contractions or shifts in the escape focus may cause some irregularities. AV conduction disturbances may result from therapy with certain drugs (e.g., agonists, opioids, digoxin), high vagal tone, or organic disease of the AV node. Diseases that have been associated with AV conduction disturbances include bacterial endocarditis (of the aortic valve), hypertrophic cardiomyopathy, infiltrative myocardial disease, and myocarditis. Idiopathic heart block may occur in middle-aged to older dogs; congenital third-degree heart block has also been seen in dogs. Symptomatic heart block is less common in cats, but evidence of any AV conduction disturbance should prompt further diagnostic evaluation. Most cases have been associated with hypertrophic cardiomyopathy. Heart block is occasionally found in old cats without detectable organic heart disease.

Type I second-degree AV block and first-degree AV block are frequently associated with high vagal tone or drug effects in dogs. These animals are often asymptomatic; exercise or injection of an anticholinergic drug (atropine or glycopyrrolate) usually abolishes the conduction disturbance. Highgrade (many blocked P waves) second-degree AV block and complete heart block usually cause lethargy, exercise intolerance, weakness, syncope, and other signs of low cardiac output. These signs become severe when the heart rate is consistently <40 beats/min. CHF develops secondary to chronic bradycardia in some dogs, especially if other cardiac disease is present.

An atropine challenge test (p. 93) is used to determine the degree of vagal influence on the AV block. Long-term oral anticholinergic therapy (e.g., propantheline bromide) can be attempted in symptomatic animals that are atropine-responsive (see Fig. 4-5). Atropine or subsequent oral anticholinergic therapy is often ineffective, however, so artificial pacing is usually indicated. An emergency infusion of dopamine (see Box 3-1) or isoproterenol may increase the ventricular escape rate in animals with high-grade second- or thirddegree block, although ventricular tachyarrhythmias may also be provoked. Oral isoproterenol is usually ineffective. A thorough cardiac workup is indicated before permanent artificial pacemaker implantation because some underlying diseases (e.g., myocardial disease, endocarditis) are associated with a poor prognosis, even after pacing. Temporary transvenous pacing is sometimes used for 1 to 2 days to assess the animal's response to a normal heart rate before permanent pacemaker surgery is performed.

# ANTIARRHYTHMIC AGENTS

Antiarrhythmic drugs can act by slowing the rate of a tachycardia, terminating a reentrant arrhythmia, or preventing abnormal impulse formation or conduction. These effects occur through modulation of tissue electrophysiologic properties and/or autonomic nervous system effects. The traditional (Vaughan-Williams) antiarrhythmic drugs are classified according to their main electrophysiologic effects on cardiac cells (Table 4-1). Although this classification system has several shortcomings (e.g., some drugs having antiarrhythmic effects are excluded, several drugs have the multiclass effects, and focus on ion channel mechanisms is lacking), clinical reference to this classification persists. See Table 4-2 and Box 4-4 for antiarrhythmic drug dosages and CRI calculation methods.

Class I agents tend to slow conduction and decrease automaticity and excitability by means of their membrane-stabilizing effects; traditional ventricular antiarrhythmic drugs belong to this class. Class II drugs include the  $\beta$ -adrenergic antagonists ( $\beta$ -blockers), which act by inhibiting the effects of catecholamines on the heart. Class III drugs prolong the effective refractory period of cardiac action potentials without decreasing conduction velocity; they may be most effective in suppressing reentrant arrhythmias and in pre-



BOX 4-4

Formulas to Calculate Constant-Rate Infusion

#### Method 1

(Allows for "fine-tuning" fluid as well as drug administration

Determine desired drug infusion rate:  $\mu g/kg/min \times kg$ body weight =  $\mu g/min (A)$ 

Determine desired fluid infusion rate: ml/hour + 60 = ml/min (B)

(A) + (B) =  $\mu$ g/min + ml/min =  $\mu$ g drug/ml of fluid Convert from  $\mu$ g to mg of drug needed (1  $\mu$ g =

Mg drug/ml fluid  $\times$  ml of fluid in bag (or bottle, etc) = mg of drug to add to the fluid container

#### Method 2

(For total dose over a 6-hour period, must also calculate fluid volume and administration rate)

Total dose in mg to infuse over a 6-hour period = Body weight (kg)  $\times$  dose ( $\mu$ g/kg/min)  $\times$  0.36

#### Method 3 (for Lidocaine)

(Faster but less helpful if fluid rate is important or fine drugdosage adjustments are needed)

For CRI of 44  $\mu g/kg/min$  of lidocaine, add 25 ml of 2% lidocaine to 250 ml of  $D_5W$ 

Infuse at 0.25 ml/25 lb of body weight/min

venting VF. Class IV drugs are the calcium entry blockers; ventricular arrhythmias are usually not responsive to these agents, but they are important against supraventricular tachyarrhythmias. Antiarrhythmic agents within this classification scheme are contraindicated in animals with complete heart block and should be used only cautiously in animals with sinus bradycardia, sick sinus syndrome, and first- or second-degree AV block.

#### **CLASS I ANTIARRHYTHMIC DRUGS**

Class I antiarrhythmic drugs block membrane Na<sup>+</sup> channels and depress the action potential upstroke (phase 0), which slows conduction velocity along the cardiac cells. They have been subclassified according to differences in other electrophysiologic characteristics. These differences (see Table 4-1) may influence their efficacy against particular arrhythmias. Most of the Class I agents depend on extracellular K<sup>+</sup> concentration for their effects, and they lose effectiveness in patients with hypokalemia.

# Lidocaine

Lidocaine HCl is usually the first-choice IV ventricular antiarrhythmic agent in dogs. It is often ineffective against supraventricular arrhythmias. It has little effect on sinus node rate, AV conduction rate, and refractoriness. Lidocaine suppresses automaticity in normal Purkinje fibers and diseased myocardial tissue, slows conduction, and reduces the



TABLE 4-1

# Classification and Effects of Antiarrhythmic Drugs

CLASSIFICATION	DRUG	MECHANISM AND ECG EFFECTS
Class I		Decreases fast inward Na <sup>+</sup> current; membrane-stabilizing effects (decreased conductivity, excitability, and automaticity)
IA	Quinidine Procainamide Disopyramide	Moderately decreases conductivity, increases action potential duration; can prolong QRS complex and Q-T interval
IB	Lidocaine Mexiletine Phenytoin	Little change in conductivity, decreases action potential duration; QRS complex and Q-T interval unchanged
IC	Flecainide Encainide Propafenone	Markedly decreases conductivity without change in action potential duration
Class II	Propranolol Atenolol Esmolol Metoprolol Carvedilol Others	β-adrenergic blockade—reduces effects of sympathetic stimulation (no direct myocardial effects at clinical doses)
Class III	Sotalol Amiodarone Ibutilide Dofetilide Others	Selectively prolongs action potential duration and refractory period; antiadrenergic effects; Q-T interval prolonged
Class IV	Verapamil Diltiazem Others	Decreases slow inward Ca <sup>++</sup> current (greatest effects on sinoatrial and AV nodes)
Other Antiarrhythmic Agents	Digoxin  Atropine Glycopyrrolate	Antiarrhythmic action results mainly from indirect autonomic effects (especially increased vagal tone) Anticholinergic agents oppose vagal effects on SA and AV nodes (glycopyrrolate and other drugs also have this effect)
	Others Adenosine	Briefly opens K <sup>+</sup> channels and indirectly slows Ca <sup>++</sup> current (greatest effects on sinoatrial and AV nodes); may transiently block AV conduction, but ineffective in dogs

AV, atrioventricular; SA, sinoatrial.

supernormal period (during which the cell can be reexcited before complete repolarization occurs). It has greater effects on diseased and hypoxic cardiac cells and at faster stimulation rates. The electrophysiologic effects of lidocaine are dependent on the extracellular potassium concentration. Hypokalemia may render the drug ineffective, but hyperkalemia intensifies its depressant effects on cardiac membranes. Lidocaine produces little or no depression of contractility at therapeutic doses when administered slowly IV; this is useful in dogs with heart failure. The lidocaine congeners tocainide and mexiletine similarly produce minimal negative inotropic and hypotensive effects. Toxic concentrations of lidocaine can cause hypotension.

Lidocaine undergoes rapid hepatic metabolism; some metabolites may contribute to its antiarrhythmic and toxic effects. Lidocaine is not effective orally because of its almost complete first-pass hepatic elimination. IV administration, usually as slow boluses followed by CRI, is most effective. Antiarrhythmic effects after IV bolus occur within 2 minutes and abate within 10 to 20 minutes. CRI without a loading dose produces steady-state concentrations in 4 to 6 hours. The half-life is <1 hour in the dog. An initial bolus of 2 mg/kg is used in dogs and can be repeated two to three times if necessary. Lower doses should be used in cats to avoid toxicity (loading dose of 0.25 to 0.5 mg/kg). The half-life in cats is 1 to 2 hours. Therapeutic plasma concentrations are thought to range from 1.5 to 6  $\mu$ g/ml in dogs. Only lidocaine without epinephrine should be used for antiarrhythmic therapy. If IV access is not possible, IM administration could be used, but IV is much preferred.

The most common toxic effect of lidocaine is central nervous system excitation. Signs include agitation,



# TABLE 4-2 Dosage of Antiarrhythmic Drugs

AGENT	DOSAGE		
Class I			
Lidocaine	Dog: initial boluses of 2 mg/kg slowly IV, up to 8 mg/kg; or rapid IV infusion at 0.8 mg/kg/min; if effective, then 25-80 μg/kg/min CRI; can also be used intratracheally for CPR Cat: initial bolus of 0.25-0.5 (or 1.0) mg/kg slowly IV; can repeat boluses of 0.15-0.25 mg/kg, up to total of 4 mg/kg; if effective, 10-40 μg/kg/min CRI		
Procainamide	Dog: 6-10 (up to 20) mg/kg IV over 5-10 minutes; 10-50 µg/kg/min CRI; 6-20 (up to 30) mg/kg IM q4-6h; 10-25 mg/kg by mouth q6h (sustained release: q6-8h) Cat: 1.0-2.0 mg/kg slowly IV; 10-20 µg/kg/min CRI; 7.5-20 mg/kg IM or by mouth q(6-)8h		
Quinidine	Dog: 6-20 mg/kg IM q6h (loading dose, 14-20 mg/kg); 6-16 mg/kg by mouth q6h; sustained action preparations, 8-20 mg/kg by mouth q8h  Cat: 6-16 mg/kg IM or by mouth q8h		
Mexiletine	Dog: 4-10 mg/kg by mouth q8h Cat: —		
Phenytoin	Dog: 10 mg/kg slowly IV; 30-50 mg/kg by mouth q8h Cat: do not use		
Propafenone	Dog: (?) 3-4 mg/kg by mouth q8h Cat: —		
Flecainide	Dog: (?) 1-5 mg/kg by mouth q8-12h Cat: —		
Class II			
Atenolol	Dog: 0.2-1.0 mg/kg by mouth q12-24h Cat: 6.25-12.5 mg/cat by mouth q(12-)24h		
Propranolol	Dog: 0.02 mg/kg initial bolus slowly IV (up to maximum of 0.1 mg/kg); initial dose, 0.1-0.2 mg/kg by mouth q8h, up to 1 mg/kg q8h  Cat: Same IV instructions; 2.5 up to 10 mg/cat by mouth q8-12h		
Esmolol	Dog: 0.1-0.5 mg/kg IV over 1 minute (loading dose), followed by infusion of 0.025-0.2 mg/kg/min Cat: same		
Metoprolol	Dog: initial dose, 0.2 mg/kg by mouth q8h, up to 1 mg/kg q8(-12)h Cat: —		
Class III			
Sotalol	Dog: 1-3.5 (-5) mg/kg by mouth q12h Cat: 10-20 mg/cat by mouth q12h (or 2-4 mg/kg by mouth q12h)		
Amiodarone	Dog: 10 mg/kg by mouth q12h for 7 days, then 8 mg/kg by mouth q24h (lower as well as higher doses have been used); 3(-5) mg/kg slowly (over 10-20 min) IV (can repeat but do not exceed 10 mg/kg in 1 hour)  Cat: —		
Class IV			
Diltiazem	Dog: Oral maintenance: initial dose 0.5 mg/kg (up to 2+ mg/kg) by mouth q8h; acute IV for supraventricular tachycardia: 0.15-0.25 mg/kg over 2-3 min IV, can repeat every 15 minutes until conversion or maximum 0.75 mg/kg; CRI: 5-15 mg/kg/hr; oral loading dose: 0.5 mg/kg followed by 0.25 mg/kg by mouth q1h to a total of 1.5(-2.0) mg/kg or conversion Cat: Same?; for HCM: 1.5-2.5 mg/kg (or 7.5-10 mg/cat) by mouth q8h; sustained-release preparations: Cardizem-CD, 10 mg/kg/day (45 mg/cat is about 105 mg of Cardizem-CD, or the amount that fits into the small end of a No. 4 gelatin capsule); Diltiazem (Dilacor) XR, 30 mg/cat/day (one half of a 60-mg controlled-release tablet within the 240-mg gelatin capsule), can increase to 60 mg/day in some cats if necessary		
Verapamil	Dog: initial dose, 0.02-0.05 mg/kg slowly IV, can repeat q5min up to a total of 0.15(-0.2) mg/kg; 0.5-2 mg/kg by mouth q8h  Cat: initial dose, 0.025 mg/kg slowly IV, can repeat every 5 minutes up to a total of 0.15(-0.2) mg/kg; 0.5-1 mg/kg by mouth q8h		



# Dosage of Antiarrhythmic Drugs-cont'd

AGENT	DOSAGE	
Anticholinergic		
Atropine	Dog: 0.02-0.04 mg/kg IV, IM, SC; can also be given intratracheally for CPR; 0.04 mg/kg by mouth q6-8h Cat: same	
	Atropine challenge test: 0.04 mg/kg IV (see text, p. 93)	
Glycopyrrolate	Dog: 0.005-0.01 mg/kg IV or IM; 0.01-0.02 mg/kg SC	
, , ,	Cat: same	
Propantheline	Dog: 3.73-7.5 mg by mouth q8-12h Cat: —	
Hyoscyamine	Dog: 0.003-0.006 mg/kg by mouth q8h Cat: —	
Sympathomimetic		
Isoproterenol	Dog: 0.045-0.09 μg/kg/min CRI Cat: same	
Terbutaline	Dog: 2.5-5 mg/dog by mouth q8-12h Cat: 1.25 mg/cat by mouth q12h	
Other Agents		
Digoxin	See Table 3-3	
Adenosine	Dog: up to 12 mg as rapid IV bolus Cat: —	
Edrophonium	Dog: 0.05 to 0.1 mg/kg IV (have atropine and endotracheal tube available) Cat: same?	
Phenylephrine	Dog: 0.004 to 0.01 mg/kg IV Cat: same?	

CRI, Constant rate infusion; CPR, cardiopulmonary resuscitation; -, effective dosage not known.

disorientation, muscle twitches, nystagmus, and generalized seizures. The latter may require diazepam (0.25 to 0.5 mg/kg IV) or a short-acting barbiturate. Nausea can also occur. Worsening of arrhythmias (a proarrhythmic effect) is seen occasionally, as it is with any drug having cardiac electrophysiologic effects. Cats are particularly sensitive to the drug's toxic effects and may undergo respiratory arrest along with seizures. In the event of toxicity, lidocaine should be discontinued until the signs of toxicity disappear; a lower infusion rate may then be instituted. IV diazepam (0.25 to 0.5 mg/kg) is used to control lidocaine-induced seizures. There are anecdotal reports of respiratory depression and arrest after the administration of lidocaine in unconscious dogs and cats. Propranolol, cimetidine, and other drugs that decrease liver blood flow slow the metabolism of lidocaine and predispose to the development of toxicity. Animals with heart failure may also have reduced hepatic blood flow and may require a lower dosage of the drug. Hepatic disease can delay elimination as well.

### **Procainamide**

Procainamide HCl has electrophysiologic effects similar to those of quinidine. Procainamide has both direct and indirect (vagolytic) effects; it is indicated for the treatment of premature ventricular (and sometimes atrial) depolarizations and tachycardias. It is less effective than quinidine in managing atrial arrhythmias and is usually not effective in converting chronic atrial flutter-fibrillation to sinus rhythm. Procainamide should be used only with caution in animals with hypotension.

Orally administered procainamide is well absorbed in the dog but has a half-life of only 2.5 to 4 hours. The sustained-release preparation has a slightly longer half-life of 3 to 6 hours. Food may delay the absorption of procainamide. The drug undergoes hepatic metabolism and renal excretion in proportion to the creatinine clearance. The metabolite N-acetylprocainamide is not clinically important in dogs and cats. Procainamide can be given orally or intramuscularly without marked hemodynamic effects, but rapid IV injection can cause hypotension and cardiac depression, although to a much lesser degree than IV quinidine. Administration by CRI can be useful if the arrhythmia responds to an IV bolus; a steady state is reached in 12 to 22 hours. Therapeutic plasma concentrations are thought to be 4 to 10 µg/ml.

The toxic effects of procainamide are similar to those of quinidine (discussed in the following section) but are usually milder. Gastrointestinal upset and prolongation of the QRS or QT intervals may occur. Procainamide can enhance the ventricular response rate to AF if used without digoxin or a β- or Ca<sup>++</sup> blocker. More serious toxic effects include hypotension, depressed AV conduction (sometimes causing second- or third-degree heart block), and proarrhythmia. The latter can cause syncope or VF. Hypotension responds to IV fluids, catecholamines, or calcium-containing solutions. Gastrointestinal signs associated with oral therapy may respond to dosage reduction. High-dose oral procainamide therapy in people has been associated with a reversible lupus-like syndrome characterized by neutropenia, fever, depression, and hepatomegaly, but this has not been documented in dogs. Long-term use can cause brown discoloration of the haircoat in black Doberman Pinschers.

#### Quinidine

Quinidine has been used to treat ventricular and, occasionally, supraventricular tachyarrhythmias. In large dogs with recent-onset AF and normal ventricular function, quinidine may cause conversion to sinus rhythm. This drug must be used cautiously in animals with heart failure or hyperkalemia. The characteristic electrophysiologic effects of quinidine are depression of automaticity and conduction velocity and prolongation of the effective refractory period. Corresponding dose-dependent ECG changes (e.g., PR, QRS, and QT prolongation) result from direct electrophysiologic and vagolytic effects. At low doses, quinidine's vagolytic effects may increase the sinus rate or the ventricular response rate to AF by antagonizing the drug's direct effects. As with other class I agents, hypokalemia reduces quinidine's antiarrhythmic effectiveness.

The drug is well-absorbed orally but has fallen out of favor for chronic oral therapy because of its frequent adverse effects and its interference with digoxin pharmacokinetics. Quinidine is metabolized extensively by the liver, with little dependence on liver blood flow. The half-life is about 6 hours in dogs and 2 hours in cats. Quinidine is highly protein-bound; severe hypoalbuminemia can predispose to toxicity. Cimetidine can also predispose to toxicity by slowing the drug's elimination. Quinidine can precipitate digoxin toxicity (when used concurrently) by displacing digoxin from skeletal muscle binding sites and reducing its renal clearance. Anticonvulsants and other drugs that induce hepatic microsomal enzymes can speed quinidine's metabolism. IV administration is not recommended because of quinidine's propensity to cause vasodilation (by means of nonspecific α-adrenergic receptor blockade), cardiac depression, and hypotension. The oral and IM routes usually do not cause adverse hemodynamic effects, but close monitoring is warranted initially, especially in animals with underlying cardiac disease. Therapeutic blood concentrations are thought to be 2.5 to  $5 \mu g/ml$  and are usually achieved in 12 to 24 hours after oral and IM administration. Slow-release sulfate (83% active drug), gluconate (62% active drug), and polygalacturonate (80% active drug) salts of quinidine prolong the drug's absorption and elimination. The sulfate salt is more rapidly absorbed than the gluconate; peak effect is usually achieved 1 to 2 hours after oral administration.

Quinidine toxicity occurs as an extension of the drug's electrophysiologic and hemodynamic actions. As the plasma concentration increases, the PR interval and QRS duration lengthen. Marked QT prolongation, right bundle-branch block, or QRS widening >25% of pretreatment value suggests drug toxicity; various conduction blocks and ventricular tachyarrhythmias are other manifestations. Marked QT prolongation implies increased temporal dispersion of myocardial refractoriness; this predisposes to torsades de pointes (see p. 25) and VF. Transient episodes of these serious arrhythmias can be a cause of syncopal attacks in people taking quinidine. Lethargy, weakness, and CHF can result from the negative inotropic and vasodilatory effects of the drug and subsequent hypotension. Cardiotoxicity and hypotension can be partially reversed by sodium bicarbonate (1 mEq/kg IV), which temporarily decreases serum K<sup>+</sup> concentration, enhances quinidine's binding to albumin, and reduces its cardiac electrophysiologic effects. Gastrointestinal signs (e.g., nausea, vomiting, diarrhea) are common with orally administered quinidine. Thrombocytopenia (reversible after quinidine discontinuation) can occur in people and possibly in dogs and cats.

#### Mexiletine

Mexiletine HCl is similar to lidocaine in its electrophysiologic, hemodynamic, toxic, and antiarrhythmic properties. It can be effective in suppressing ventricular tachyarrhythmias in dogs. The combination of a β-blocker (or procainamide or quinidine) with mexiletine may be more efficacious and associated with fewer adverse effects than mexiletine alone. The drug is easily absorbed when administered orally, but antacids, cimetidine, and narcotics reportedly slow its absorption in people. Mexiletine undergoes hepatic metabolism (influenced by liver blood flow) and some renal excretion (which is slower if the urine is alkaline). Hepatic microsomal enzyme inducers may accelerate its clearance. The half-life in dogs is from 4.5 to 7 hours (depending to some degree on the urine pH). Approximately 70% of the drug is protein bound. The therapeutic serum concentration is thought to range from 0.5 to 2.0  $\mu$ g/ml (as in people). The effects of this drug in cats are not known. Adverse effects have included vomiting, anorexia, tremor, disorientation, sinus bradycardia, and thrombocytopenia. Overall, mexiletine appears to produce fewer adverse effects than tocainide.

### Phenytoin

Phenytoin's electrophysiologic effects are similar to those of lidocaine. It also has some slow-calcium channel inhibitory and central nervous system effects that may contribute to its effectiveness against digitalis-induced arrhythmias. This drug is currently used only for digitalis-induced ventricular arrhythmias that have not responded to lidocaine in dogs. Its contraindications are the same as for lidocaine. Slow IV infusion and oral administration do not cause relevant hemodynamic disturbances; however, the oral bioavailability of phenytoin is poor. Rapid IV injection should be avoided

because the propylene glycol vehicle can depress myocardial contractility, exacerbate arrhythmias, and cause vasodilation, hypotension, or respiratory arrest. The half-life of phenytoin in the dog is about 3 hours. The drug is metabolized in the liver, and it may speed up its own elimination by stimulating hepatic microsomal enzymes. Co-administration of cimetidine, chloramphenicol, and other drugs that inhibit microsomal enzyme activity increases phenytoin's serum concentration. The IV administration of phenytoin has been associated with bradycardia, AV blocks, ventricular tachycardia, and cardiac arrest. Other manifestations of phenytoin toxicity include central nervous system signs (e.g., depression, nystagmus, disorientation, ataxia). The drug is not used in cats because its half-life is >40 hours, and even low doses produce toxic serum concentrations in this species.

# Other Class I Agents

Disopyramide is similar to quinidine and procainamide electrophysiologically. It has a very short half-life in the dog (<2 hours), as well as marked depressive effects on the canine myocardium. Tocainide, a class IB agent similar to lidocaine, is no longer available in the United States. Flecainide and propafenone are class IC agents. They produce marked reduction in cardiac conduction velocity but have little effect on sinus rate or refractoriness. High doses depress automaticity in the sinus node and specialized conducting tissues. Vasodilation and myocardial depression can result in severe hypotension after IV injection, especially in animals with underlying cardiac disease. Proarrhythmia is a serious potential adverse effect of these agents. Bradycardia, intraventricular conduction disturbance, and consistent (although transient) hypotension, as well as nausea, vomiting, and anorexia, have occurred in dogs. Flecainide (and encainide) have been associated with increased mortality in people. These agents are rarely (and cautiously) used for treating life-threatening ventricular arrhythmias refractory to other therapy.

# CLASS II ANTIARRHYTHMIC DRUGS: β-ADRENERGIC BLOCKERS

Class II antiarrhythmic drugs act by blocking catecholamine effects. They slow heart rate, reduce myocardial O2 demand, and increase AV conduction time and refractoriness. The antiarrhythmic effect of β-blockers relates to β<sub>1</sub>-receptor blockade rather than direct electrophysiologic effects. They are often used in combination with a class I agent (e.g., procainamide or mexiletine), although their negative inotropic effect demands caution when used in animals with myocardial failure. B-receptor blockers are used in animals with hypertrophic cardiomyopathy, certain congenital and acquired ventricular outflow obstructions, systemic hypertension, hyperthyroid heart disease, supraventricular and ventricular tachyarrhythmias (especially those induced by enhanced sympathetic tone), and other diseases or toxicities that cause excessive sympathetic stimulation. A \(\beta\)-blocker is often used in conjunction with digoxin to slow the ventricular response rate to AF. A β-blocker such as propranolol or atenolol is considered the first-line antiarrhythmic agent in cats for the treatment of both supraventricular and ventricular tachyarrhythmias. In people with stable heart failure, long-term therapy with certain \( \beta \)-blockers improves cardiac function and prolongs survival in those who tolerate the drug (see p. 69).

β-adrenergic receptors have been classified into subtypes.  $\beta_1$ -receptors are located primarily in the myocardium and mediate increases in contractility, heart rate, AV conduction velocity, and automaticity in specialized fibers. Extracardiac  $\beta_2$ -receptors mediate bronchodilation and vasodilation, as well as renin and insulin release. There are also some  $\beta_2$ - as well as  $\beta_3$ -receptors in the heart. "Nonselective"  $\beta$ -blockers inhibit catecholamine binding to both  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. Other  $\beta$ -blockers are more selective; they antagonize mainly one or the other receptor subtype (Table 4-3). The first-generation  $\beta$ -blockers (e.g., propranolol) have nonselective  $\beta$ -blocking effects. Second-generation agents



Characteristics of Selected \( \beta \)-Blockers

DRUG	ADRENERGIC RECEPTOR SELECTIVITY	LIPID SOLUBILITY	MAIN ROUTE OF ELIMINATION
Atenolol	$eta_1$	0	RE
Carvedilol	$\beta_1, \beta_2, \alpha_1$	+	HM
Esmolol	$\beta_1$	О	BE
Labetalol	$\beta_1, \beta_2, \alpha_1$	++	HM
Metoprolol	$\beta_1$	++	HM
Nadolol	$\beta_1$ , $\beta_2$	0	RE
Pindolol*	$\beta_1$ , $\beta_2$	++	В
Propranolol	$\beta_1$ , $\beta_2$	++	HM
Sotalol**	$\beta_1, \beta_2$	0	RE
Timolol	$\beta_1, \beta_2$	0	RE

<sup>\*</sup> Has intrinsic sympathomimetic activity.

<sup>\*\*</sup> Also has class III antiarrhythmic activity.

RE, Renal excretion; BE, blood esterases; HM, hepatic metabolism; B, both renal excretion and hepatic metabolism are important.

(e.g., atenolol, metoprolol) are relatively  $\beta_1$  selective. The third-generation  $\beta$ -blockers affect both  $\beta_1$  and  $\beta_2$  receptors but also antagonize  $\alpha_1$  receptors and may have other effects. A few  $\beta$ -blockers have some degree of intrinsic sympathomimetic activity.

The clinical antiarrhythmic effect of class II drugs is thought to relate to  $\beta_1$ -receptor blockade rather than to direct electrophysiologic mechanisms. In normal animals β-receptor blockers have little negative inotropic effect. However, they must be used cautiously in animals with underlying myocardial disease because increased sympathetic drive may be needed to maintain cardiac output. Marked depression of cardiac contractility, conduction, or heart rate can result in such cases. β-blockers are generally contraindicated in patients with sinus bradycardia, sick sinus syndrome, high-grade AV block, or severe CHF and in animals also receiving a Ca+1-blocking drug. Nonselective β-blockers may increase peripheral vascular resistance (because of unopposed  $\alpha$ -adrenergic effects) and provoke bronchoconstriction. β-blockers may also mask the early signs of acute hypoglycemia in diabetics (e.g., tachycardia and blood pressure changes), and reduce the release of insulin in response to hyperglycemia. Because the effect of β-blockers depends on the level of sympathetic activation, individual patient response is quite variable. Therefore initial dosages should be low and cautiously titrated upward as needed.

β-blockers enhance the depression of AV conduction produced by digitalis, class I antiarrhythmic drugs, and Ca<sup>++</sup>-blockers. Use of a β-blocker and a Ca<sup>++</sup>-blocker simultaneously can markedly decrease heart rate and myocardial contractility. Because of possible β-receptor upregulation (increased number or affinity of receptors) during long-term  $\beta$ -blockade, therapy should not be abruptly discontinued.

#### **Propranolol**

Propranolol HCl is a nonselective  $\beta$ -blocker that was widely used in dogs and cats, although atenolol is used more often now. Propranolol is not recommended for patients with pulmonary edema because of the potential for bronchoconstriction caused by  $\beta_2$ -receptor antagonism. The  $\beta_2$ -receptor blocking effects of propranolol also make it relatively contraindicated in patients with asthma or chronic small airway disease.

Propranolol undergoes extensive first-pass hepatic metabolism, so oral bioavailability is low; but with time and use of higher doses hepatic enzymes become saturated and bioavailability increases. Propranolol reduces hepatic blood flow, which prolongs its elimination as well as that of other drugs dependent on liver blood flow for their metabolism (e.g., lidocaine). Feeding delays oral absorption and increases drug clearance after IV dosing (by increasing hepatic blood flow). The half-life of propranolol in the dog is only about 1.5 hours (0.5 to 4.2 hours in cats). Active metabolites exist and dosing every 8 hours appears to be adequate in both species. IV propranolol is used mainly for refractory ventricular tachycardia (in conjunction with a class I

drug) and for emergency treatment of atrial or junctional tachycardia.

Toxicity is most often related to excessive  $\beta$ -blockade; this can develop at relatively low doses in some animals. Bradycardia, heart failure, hypotension, bronchospasm, and hypoglycemia can occur. Infusion of a catecholamine (e.g., dopamine or dobutamine) will help reverse these effects. Propranolol and other lipophilic  $\beta$ -blockers can cause central nervous system effects such as depressed attitude and disorientation.

#### **Atenolol**

Atenolol is a selective  $\beta_1$ -blocker. It is used commonly to slow sinus rate and AV conduction and to suppress ventricular premature beats. The half-life of atenolol is slightly more than 3 hours in dogs and about 3.5 hours in cats. Its oral bioavailability in both species is high (~90%). Atenolol is excreted in the urine, so renal dysfunction delays its clearance. Atenolol's  $\beta$ -blocking effect lasts more than 12 hours but less than 24 hours in normal cats. This drug is hydrophilic. Adverse central nervous system effects are unlikely because it does not readily cross the blood-brain barrier. As with other  $\beta$ -blockers, weakness or exacerbation of heart failure can occur.

# Metoprolol

Metoprolol tartrate is another  $\beta_1$ -selective agent. It is well absorbed orally, but bioavailability is reduced by a large first-pass effect. There is minimal protein-binding. The drug is metabolized in the liver and excreted in the urine. Half-life is 1.6 hours in dogs and 1.3 hours in cats. Metoprolol has been used in some dogs with dilated cardiomyopathy and chronic valvular disease. It may possibly contribute to improved cardiac function over time (see p. 69).

#### Esmolol

Esmolol HCl is an ultra-short acting  $\beta_1$ -selective agent. It is rapidly metabolized by blood esterases and has a half-life of <10 minutes. Steady state occurs in 5 minutes after a loading dose or 30 minutes without. Esmolol's effects are gone within 10 to 20 minutes after infusion is terminated. This drug is used for acute therapy of tachyarrhythmias and feline hypertrophic obstructive cardiomyopathy.

# Other **B-Blockers**

Many other  $\beta$ -blocking drugs are available. Their receptor selectivity as well as their pharmacologic characteristic vary. Certain  $\beta$ -blockers may prove useful in patients with chronic, stable myocardial failure by reducing the cardiotoxic effects of excessive sympathetic stimulation, improving cardiac function, promoting upregulation of cardiac  $\beta$ -receptors, and increasing survival time (see p. 69). The third-generation  $\beta$ -blocker, carvedilol, and the second-generation agent, metoprolol, are effective in this regard. Nonselective (first-generation) agents, such as propranolol, and some later-generation agents do not appear to confer these survival benefits.

Agents with intrinsic sympathomimetic activity appear to have deleterious effects.

# CLASS III ANTIARRHYTHMIC DRUGS

Common features of class III drugs include prolongation of the cardiac action potential and effective refractory period without a decrease in conduction velocity. Their effects are mediated by inhibition of potassium channels responsible for repolarization (delayed rectifier current). These agents are useful for ventricular arrhythmias, especially those caused by reentry. Class III drugs have antifibrillatory effects as well. They share some characteristics of other antiarrhythmic drug classes in addition to their class III effects.

#### Sotalol

Sotalol HCl is a nonselective  $\beta$ -blocker that has Class III effects at higher doses. Its oral bioavailability is high, although absorption is reduced when given with food. Sotalol's halflife is about 5 hours in dogs. It is eliminated unchanged by the kidneys, and renal dysfunction prolongs elimination. Sotalol's \( \beta\)-blocking effect outlasts its plasma half-life. The drug has minimal hemodynamic effects, although it can cause slowed sinus rate, first-degree AV block, and hypotension. Proarrhythmia can occur (as with all antiarrhythmic agents), including torsades de pointes. Sotalol's class III effects occur at higher doses in dogs than in people. Doses used clinically in dogs may be producing primarily β-blocking effects. On the other hand, a high incidence of proarrhythmia (especially torsades de pointes), of concern in people taking sotalol, has not been reported clinically in dogs. Experimentally, in dogs with hypokalemia, coadministration of mexiletine reduced the proarrhythmic potential.

Sotalol may worsen heart failure in animals with dilated cardiomyopathy. However, sotalol is thought to have less negative inotropic effect than propranolol. Other adverse effects of sotalol have included hypotension, depression, nausea, vomiting, diarrhea, and bradycardia. There are occasional anecdotal reports of aggression that resolved after sotalol was discontinued.

### **Amiodarone**

Amiodarone HCl is thought to produce its antiarrhythmic effects by prolonging the action potential duration and effective refractory period in both atrial and ventricular tissues. Although considered a class III agent, it shares properties with all three other antiarrhythmic drug classes. Amiodarone is an iodinated compound that also has noncompetitive  $\alpha_{t^-}$  and  $\beta$ -blocking effects, as well as  $Ca^{++}$  channel-blocking effects. The  $\beta$ -blocking effects occur soon after administration, but maximal class III effects (and prolongation of action potential duration and QT interval) are not achieved for weeks with chronic administration. Its  $Ca^{++}$  blocking effects may inhibit triggered arrhythmias by reducing afterdepolarizations. Therapeutic doses slow the sinus rate, decrease AV conduction velocity, and minimally depress myocardial contractility and blood pressure. Indications for

amiodarone include refractory atrial and ventricular tachyarrhythmias, especially reentrant arrhythmias using an accessory pathway. The IV form is used in people with AF, ventricular tachycardia, and during cardiopulmonary resuscitation from recurrent ventricular tachycardia and fibrillation; similar applications are expected in dogs. However, conservative dosing with slow injection over 10 to 20 minutes is recommended, because IV use can cause hypotension and bradycardia. The drug is also given by CRI in people; 10 to 15 mg/kg/day has been used in children.

The pharmacokinetics of amiodarone are complex. Chronic oral use is associated with a prolonged time to steady state (of several weeks), concentration of drug in myocardial and other tissues, and accumulation of an active metabolite (desethylamiodarone). Therapeutic serum concentration is thought to be 1 to 2.5  $\mu$ g/ml. Amiodarone may have less of a proarrhythmic effect than other agents and may reduce the risk of sudden death because of uniform prolongation of repolarization throughout the ventricles, as well as suppression of Purkinje fiber automaticity. In normal dogs IV amiodarone does not adversely affect contractility at cumulative doses less than 12.5 to 15 mg/kg. However, the potential exists for more profound cardiac depression and hypotension in dogs with myocardial disease. Amiodarone use is not described in cats.

Long-term amiodarone is associated with many potential adverse effects, including depressed appetite, gastrointestinal upset, pneumonitis leading to pulmonary fibrosis, hepatopathy, thyroid dysfunction, positive Coombs test, thrombocytopenia, and neutropenia. Occasional hypersensitivity reactions (with acute angioedema formation) or of tremors have occurred in dogs. Other adverse effects observed in people have included corneal microdeposits, photosensitivity, bluish skin discoloration, and peripheral neuropathy. Amiodarone can increase the serum concentration of digoxin, diltiazem, and possibly procainamide and quinidine.

# Other Class III Agents

Ibutilide fumarate is somewhat effective for converting recent-onset AF in people, but there is little veterinary experience with this drug. In experimental rapid-pacing—induced cardiomyopathy in dogs, ibutilide caused episodes of torsades de pointes.

Dofetilide is another drug that selectively blocks the rapid component of the K' current responsible for repolarization. It too is used in people for the conversion of AF and to maintain sinus rhythm. Its efficacy for this appears to be comparable to that of other class III drugs, and it does not exacerbate left ventricular dysfunction. Bretylium tosylate is no longer available in the United States.

# CLASS IV ANTIARRHYTHMIC DRUGS: CALCIUM ENTRY BLOCKERS

The Ca<sup>++</sup> entry blockers are a diverse group of drugs that have the common property of decreasing cellular Ca<sup>++</sup> influx by blocking transmembrane L-type calcium channels. As a

group, these drugs can cause coronary and systemic vasodilation, enhance myocardial relaxation, and reduce cardiac contractility. Some calcium entry blockers have antiarrhythmic effects, especially on tissues dependent on the slow inward Ca<sup>++</sup> current, such as the sinus and AV nodes. Other conditions for which calcium entry blockers are potentially useful include hypertrophic cardiomyopathy, myocardial ischemia, and hypertension.

Possible adverse effects of these agents include reduced contractility, vasodilation, hypotension, depression, anorexia, lethargy, bradycardia, and AV block. Low initial doses are used and increased as needed to effect or to maximal recommended dose. Contraindications to  $Ca^{++}$  channel blocker use include sinus bradycardia, AV block, sick sinus syndrome, digoxin toxicity, and myocardial failure (for agents with pronounced negative inotropic effect). They are usually not prescribed in patients receiving a  $\beta$ -blocker because of additive negative effects on contractility, AV conduction, and heart rate. An overdose or exaggerated response to a  $Ca^{++}$  blocker is treated with supportive care, including atropine for bradycardia or AV block, dopamine or dobutamine (see Box 3-1) and furosemide for heart failure, and dopamine or IV calcium salts for hypotension.

# **Diltiazem**

Diltiazem HCl is a benzothiazepine Ca<sup>-+</sup> channel blocker. It slows AV conduction, causes potent coronary and mild peripheral vasodilation, and has a lesser negative inotropic effect than the prototypical calcium entry blocker, verapamil. Diltiazem is often combined with digoxin to further slow the ventricular response rate to AF in dogs. It is indicated for other supraventricular tachyarrhythmias as well. Diltiazem is often used in cats with hypertrophic cardiomyopathy; its beneficial effects can include enhanced myocardial relaxation and perfusion, as well as a mild decrease in heart rate, contractility, and myocardial oxygen demand (see Chapter 8). Chronic diltiazem therapy may be associated with a decrease in left ventricular wall and septal thickness in cats with hypertrophic cardiomyopathy.

Peak effects are seen within 2 hours of oral dosing, and the effects last at least 6 hours in dogs. Extensive first-pass effect limits bioavailability, especially in dogs. The half-life of diltiazem in the dog is just over 2 hours, but chronic oral treatment prolongs it because of enterohepatic circulation. In cats plasma diltiazem concentration peaks in 30 minutes, and the effects last for 8 hours. The therapeutic range is 50 to 300 ng/ml. Diltiazem is metabolized in the liver; active metabolites exist. Drugs that inhibit hepatic enzyme systems (e.g., cimetidine) decrease the metabolism of diltiazem. Propranolol and diltiazem reduce each other's clearance when used simultaneously. A sustained-release preparation (Cardizem-CD), at 10 mg/kg daily in cats, produces plasma concentrations that peak in 6 hours and remain in the therapeutic range for 24 hours. A dose of 45 mg per cat is approximately equal to 105 mg of Cardizem-CD (or the amount that fits into the small end of a No. 4 gelatin capsule; a 300-mg capsule provides about 6.5 doses); this is given once daily. Diltiazem XR is another sustainedrelease diltiazem preparation. The 240-mg capsule contains four 60-mg tablets. There is much intercat variability in pharmacokinetics with this form. Higher doses are more likely to be associated with anorexia and other gastrointestinal signs.

Adverse effects of diltiazem are uncommon at therapeutic doses, although anorexia, nausea, and bradycardia may occur. Rarely, other gastrointestinal, cardiac, and neurologic adverse effects develop. High liver enzyme activities and anorexia occur sporadically in cats. Some cats have become aggressive or shown other personality change when treated with diltiazem.

# Verapamil

Verapamil HCl is a phenylalkylamine and has the most potent cardiac effects of the Ca<sup>++</sup>-blockers used clinically. The drug increases the refractory period of nodal tissues and can abolish reentrant SVT as well as slow the ventricular response rate in AF. Verapamil causes dose-related slowing of the sinus rate and AV conduction. It is sometimes used for supraventricular and atrial tachycardias in animals without heart failure. Verapamil's half-life in dogs is about 2.5 hours. It is poorly absorbed and undergoes first-pass hepatic metabolism, resulting in low bioavailability with oral use. The pharmacokinetics in cats are similar to those of dogs.

The drug has important negative inotropic and some vasodilatory effects that can cause cardiac decompensation, hypotension, and even death in the presence of underlying myocardial disease. An initially low IV dose is given very slowly; this can be repeated at 5- (or more) minute intervals if no adverse effects have occurred and the arrhythmia persists. Blood pressure monitoring is advisable because of the potential for hypotension. As discussed above, verapamil is not recommended for use in animals with heart failure. The toxic effects of verapamil include sinus bradycardia, AV block, hypotension, reduced myocardial contractility, and cardiogenic shock. Verapamil reduces the renal clearance of digoxin.

# Other Calcium Channel Blockers

A number of other Ca<sup>++</sup>-blockers are available. Most (dihydropyridine group) are used as antihypertensives. Amlodipine besylate is recommended as the first-line antihypertensive agent in cats and is also used in some hypertensive dogs (see Chapter 11). Amlodipine is also used in the treatment of chronic refractory heart failure in some dogs (see Table 3-3). The drug is not useful as an antiarrhythmic agent. Nifedipine is another potent vasodilator without antiarrhythmic effects.

# ANTICHOLINERGIC DRUGS Atropine and Glycopyrrolate

Anticholinergic drugs increase sinus node rate and AV conduction when vagal tone is increased (see Table 4-2). Parenteral atropine or glycopyrrolate is indicated for bradycardia

or AV block induced by anesthesia, central nervous system lesions, and certain other diseases or toxicities. Atropine is a competitive muscarinic receptor antagonist that is used to determine whether excess vagal tone is responsible for arrhythmias attributed to sinus and/or AV nodal dysfunction. This is known as the atropine challenge test (or atropine response test). Response to atropine challenge is most consistent with IV administration of 0.04 mg/kg. An ECG is recorded within 5 to 10 minutes after atropine injection. If the heart rate has not increased by at least 150%, the ECG is repeated 15 (to 20) minutes after atropine injection; sometimes, an initial vagomimetic effect on the AV node lasts longer than 5 minutes. The normal sinus node response is a rate increase to 150 to 160 beats/minute (or >135 beats/ minute). A positive response may not predict response to oral anticholinergic therapy. Atropine has little to no effect on bradyarrhythmias caused by intrinsic disease of the sinus or AV node.

Atropine given by any parenteral route can transiently exacerbate vagally mediated AV block when the atrial rate increases faster than AV conduction can respond. However, IV administration causes the fastest and most consistent onset and resolution of the exacerbated block, as well as the most rapid postbradycardia heart rates, compared with the IM and subcutaneous routes. Unlike atropine, glycopyrrolate does not have centrally mediated effects, and its effects are longer-lasting than those of atropine.

# Oral Anticholinergic Drugs

Some animals that respond to parenteral atropine or glycopyrrolate will also respond to an oral anticholinergic agent. Clinical signs may be relieved in these animals, at least for a time. Nevertheless, animals with symptomatic bradyarrhythmias usually require permanent pacemaker implantation to effectively control heart rate. Propantheline bromide and hyoscyamine sulfate are commonly used, but other oral anticholinergic agents are also available. Individual dosage is adjusted to effect. Oral absorption of propantheline is variable; food may decrease drug absorption.

Vagolytic drugs can aggravate paroxysmal supraventricular tachyarrhythmias (as in sick sinus syndrome) and should be used only cautiously as chronic therapy in those patients. Other adverse effects of anticholinergic therapy include vomiting, dry mouth, constipation, keratoconjunctivitis sicca, increased intraocular pressure, and drying of respiratory secretions.

#### SYMPATHOMIMETIC DRUGS

Isoproterenol HCl is a  $\beta$ -receptor agonist that has been used to treat symptomatic AV block or bradycardia refractory to atropine, although electrical pacing is safer and more effective. It also can be effective for torsades de pointes. Because of its affinity for  $\beta_2$ -receptors, isoproterenol can cause hypotension. It is not used for treating either heart failure or cardiac arrest. Isoproterenol can be arrhythmogenic, as can other catecholamines. The lowest effective dose (see Table 4-2) is used, and the animal is monitored closely for arrhyth-

mias. Oral administration is not effective because of marked first-pass hepatic metabolism.

Terbutaline sulfate is a  $\beta_2$ -receptor agonist that may have a mild stimulatory effect on heart rate when given orally. Methylxanthine bronchodilators (e.g., aminophylline and theophylline) increase heart rate in some dogs with sick sinus syndrome when used at higher doses.

#### OTHER DRUGS

Edrophonium chloride is a short-acting anticholinesterase with nicotinic and muscarinic effects. Although mainly used for diagnosing myasthenia gravis, it slows AV conduction, which can help in the diagnosis and resolution of some cases of acute SVT. The drug's effect begins within 1 minute and lasts up to 10 minutes after IV injection. Adverse effects are primarily cholinergic and include gastrointestinal (e.g., vomiting, diarrhea, salivation), respiratory (e.g., bronchospasm, respiratory paralysis, edema), cardiovascular (e.g., bradycardia, hypotension, cardiac arrest), and muscular (e.g., twitching, weakness) signs. Atropine and supportive care are used if necessary.

Phenylephrine HCl is an α-adrenergic agonist that increases blood pressure by peripheral vasoconstriction. A baroreflex-mediated increase in vagal tone slows AV conduction and is thought to underlie its effects on SVT. Phenylephrine's pressor effect begins rapidly after IV injection and persists for up to 20 minutes. The drug is contraindicated in patients with hypertension or ventricular tachycardia. Extravasation can cause ischemic necrosis of surrounding tissue

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# CHAPTER

# Congenital Cardiac Disease



# **CHAPTER OUTLINE**

GENERAL CONSIDERATIONS
EXTRACARDIAC ARTERIOVENOUS SHUNT

Patent Ductus Arteriosus

VENTRICULAR OUTFLOW OBSTRUCTION

Subaortic Stenosis

**Pulmonic Stenosis** 

INTRACARDIAC SHUNT

Ventricular Septal Defect

Atrial Septal Defect

ATRIOVENTRICULAR VALVE MALFORMATION

Mitral Dysplasia

Tricuspid Dysplasia

CARDIAC ANOMALIES CAUSING CYANOSIS

Tetralogy of Fallot

Pulmonary Hypertension with Shunt Reversal

OTHER CARDIOVASCULAR ANOMALIES

Vascular Ring Anomalies

Cor Triatriatum

**Endocardial Fibroelastosis** 

Other Vascular Anomalies

#### **GENERAL CONSIDERATIONS**

Common congenital cardiac malformations, as well as some that occur more sporadically, are described in this chapter. Most congenital heart defects produce an audible murmur (Fig. 5-1), although some serious malformations do not. Murmurs caused by congenital disease range in intensity from very loud to very soft depending on the type and severity of the defect and on hemodynamic factors. In addition to murmurs of congenital disease, clinically insignificant "innocent" murmurs are relatively common in puppies and kittens. Innocent murmurs are usually soft systolic ejection—type murmurs heard best at the left heart base; their intensity may vary with heart rate or body position. Innocent murmurs tend to get softer and usually disappear by about 4 months

of age. Murmurs caused by congenital disease usually persist and may get louder with time, although this is not always the case. Careful examination and auscultation are important, not only in animals intended for breeding but also in working dogs and pets. Puppies and kittens with a soft murmur and no other clinical or radiographic signs can be ausculted repeatedly as they grow to determine if the murmur disappears. Further diagnostic tests are indicated in animals with a persistent or loud murmur, those that manifest other signs, and those for which economic or breeding-potential decisions are pending. Adult dogs and cats with a previously undiagnosed congenital defect may or may not manifest clinical signs of disease at presentation.

Congenital heart defects most often involve either a valve (or valve region) or an abnormal communication between the systemic and pulmonary circulations. Abnormally formed valves can be insufficient, stenotic, or both. Other malformations can exist, and multiple anomalies occur in some patients. Congenital malformations vary widely in type and severity. The patient's prognosis and options for therapy depend on the definitive diagnosis as well as severity. Initial noninvasive testing usually includes thoracic radiographs, an electrocardiogram (ECG), and echocardiographic studies (M-mode, 2-dimensional [2-D], and Doppler). A packed cell volume (PCV) documents erythrocytosis in some cases with right-to-left shunting. Cardiac catheterization with selective angiocardiography can be useful to define some structural abnormalities or severity and is needed during transvascular interventional procedures. Surgical repair or palliation, balloon valvuloplasty, transcatheter shunt occlusion, or other interventional techniques may be helpful for some cases.

Patent ductus arteriosus (PDA) and subaortic stenosis (SAS) have been identified in different surveys as the most common congenital cardiovascular anomaly in the dog; pulmonic stenosis (PS) is also quite common. Persistent right aortic arch (a vascular ring anomaly), ventricular septal defect (VSD), malformations (dysplasia) of the atrioventricular (AV) valves, atrial septal defect (ASD), and tetralogy of Fallot (T of F) occur less frequently but are not rare. An AV septal (endocardial cushion) defect consists of all or

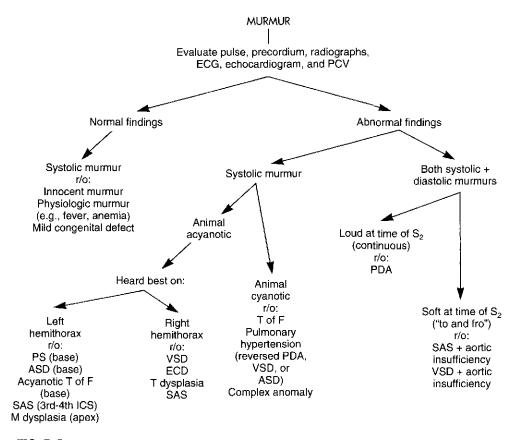


FIG 5-1

Flow chart for differentiating murmurs in puppies and kittens. ASD, Atrial septal defect; ECD, endocardial cushion defect; ECG, electrocardiogram; ICS, intercostal space; M, mitral valve; PCV, packed cell volume; PDA, patent ductus arteriosus; r/o, rule out; SAS, subaortic stenosis; T, tricuspid valve; T of F, tetralogy of Fallot; VSD, ventricular septal defect.

some of the following: a high VSD, a low ASD, and malformations of one or both AV valves. The most common malformations in cats are AV valve dysplasias and atrial or ventricular septal defects; other lesions include SAS, PDA, T of F, and PS. Endocardial fibroelastosis, mainly in Burmese and Siamese cats, also has been reported. Congenital malformations are more prevalent in male than female cats. Congenital malformations in both species can occur as isolated defects, which is most often the case, or in various combinations.

The prevalence of congenital defects is higher in purebred animals than in mixed-breed animals. In some studies a polygenic inheritance pattern has been suggested, although there is more recent focus on a single major gene effect influenced by other modifying genes. Recognized breed predispositions are listed in Table 5-1; animals of other breeds can also be affected with any of these defects as well.

# EXTRACARDIAC ARTERIOVENOUS SHUNT

The most common congenital arteriovenous shunt is PDA. Rarely, similar hemodynamic and clinical abnormalities are caused by an aorticopulmonary window (a communication between the ascending aorta and pulmonary artery) or some other functionally similar communication in the hilar region.

#### **PATENT DUCTUS ARTERIOSUS**

# **Etiology and Pathophysiology**

Functional closure of the ductus arteriosus normally occurs within hours after birth and is followed by structural changes that occur over several months, which cause permanent closure. The ductal wall in animals with an inherited PDA is histologically abnormal and unable to constrict. When the ductus fails to close, blood shunts through it from the descending aorta into the pulmonary artery. Shunting occurs during both systole and diastole because aortic pressure normally is higher than pulmonic pressure throughout the cardiac cycle. This left-to-right shunt causes a volume overload of the pulmonary circulation, left atrium (LA), and left ventricle (LV). The shunt volume is directly related to the pressure difference (gradient) between the two circulations and the diameter of the ductus.

Hyperkinetic arterial pulses are characteristic of PDA. Blood runoff from the aorta into the pulmonary system allows diastolic aortic pressure to decrease below normal.



TABLE 5-1

# Breed Predispositions for Congenital Heart Disease

DISEASE	BREED	
Patent ductus arteriosus	Maltese, Pomeranian, Shetland Sheepdog, English Springer Spaniel, Keeshond, Bichon Frise, Toy and Miniature Poodles, Yorkshire Terrier, Collie, Cocker Spaniel, German Shepherd Dog; Chihuahua, Kerry Blue Terrier, Labrador Retriever, Newfoundland; female > male	
Subaortic stenosis	Newfoundland, Golden Retriever, Rottweiler, Boxer, German Shepherd Dog, English Bulldog, Great Dane, German Short-Haired Pointer, Bouvier des Flandres, Samoyed	
Pulmonic stenosis	Bulldog (male > female), Mastiff, Samoyed, Miniature Schnauzer, West Highland White Terrier, Cocker Spaniel, Beagle, Airedale Terrier, Boykin Spaniel, Chihuahua, Scottish Terrier, Boxer, Fox Terrier(?)	
Ventricular septal defect	English Bulldog, English Springer Spaniel, Keeshond; cats	
Atrial septal defect	Samoyed, Doberman Pinscher, Boxer	
Tricuspid dysplasia	Labrador Retriever, German Shepherd Dog, Boxer, Weimaraner, Great Dane, Old English Sheepdog, Golden Retriever; other large breeds; (male > female?)	
Mitral dysplasia	Bull Terrier, German Shepherd Dog, Great Dane, Golden Retriever, Newfoundland, Mastiff, Rottweiler(?); cats; (male > female)	
Tetralogy of Fallot	Keeshond, English Bulldog	
Persistent right aortic arch	German Shepherd Dog, Great Dane, Irish Setter	

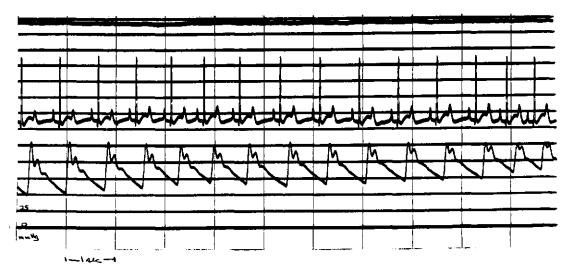


FIG 5-2

Continuous femoral artery pressure recording during surgical ligation of a patent ductus arteriosus in a Poodle. The wide pulse pressure (left side of trace) narrows as the ductus is closed (right side of trace). Diastolic arterial pressure rises because blood runoff into the pulmonary artery is curtailed. (Courtesy Dr. Dean Riedesel.)

The widened pulse pressure (systolic minus diastolic pressure) causes palpably stronger arterial pulses (Fig. 5-2),

Compensatory mechanisms (e.g., increased heart rate, volume retention) maintain adequate systemic blood flow. However, the l.V is subjected to a great hemodynamic burden, especially when the ductus is large, because the increased stoke volume is pumped into the relatively high pressure aorta. l.V and mitral annulus dilation in turn cause mitral regurgitation and further volume overload. Excess fluid retention, declining myocardial contractility

stemming from the chronic volume overload, and arrhythmias contribute to the development of congestive heart failure (CHF).

In some cases, excessive pulmonary blood flow leads to pulmonary vascular changes, increased resistance, and pulmonary hypertension (see p. 109). If pulmonary artery pressure rises to equal aortic pressure, very little blood shunting occurs. However, if pulmonary artery pressure exceeds aortic pressure, shunt reversal (right-to-left flow) occurs. Approximately 15% of dogs with inherited PDA develop a reversed

shunt; female Cocker Spaniels may be at increased risk for reversed PDA.

#### **Clinical Features**

A left-to-right shunting PDA (discussed here) is by far the most common form; clinical features of reversed PDA are described on p. 110. The prevalence of PDA is higher in certain breeds of dogs, and a polygenic inheritance pattern is thought to be responsible. The prevalence is approximately three times greater in female than male dogs. Reduced exercise ability, tachypnea, or cough is present in some cases, but many animals are asymptomatic when first diagnosed. Typical findings include a continuous murmur heard best high at the left base (see p. 9), often with a precordial thrill, hyperkinetic (bounding, "waterhammer") arterial pulses, and pink mucous membranes.

# Diagnosis

Radiographs usually show cardiac clongation (left heart dilation), left atrial and auricular enlargement, and pulmonary overcirculation (Table 5-2). A bulge often is evident in the descending aorta ("ductus bump") or main pulmonary trunk, or both (Fig. 5-3). The triad of all three bulges (i.e., pulmonary trunk, aorta, and left auricle), located in that order from the 1 to 3 o'clock position on a dorsoventral (DV) radiograph, is a classic finding but not always seen. There is also evidence of pulmonary edema in animals with left-sided heart failure. Characteristic ECG findings include wide P waves, tall R waves, and often deep Q waves in leads II, aVF, and CV<sub>6</sub>LL. Changes in the ST-T segment secondary

to LV enlargement may occur. However, the ECG is normal in some animals with PDA.

Echocardiography also shows left heart enlargement and pulmonary trunk dilation. LV fractional shortening can be normal or decreased, and the E point-septal separation is often increased. The ductus itself may be difficult to visualize because of its location between the descending aorta and pulmonary artery. Views from the cranial left parasternal position are useful. Doppler interrogation documents continuous, turbulent flow into the pulmonary artery (Fig. 5-4). The maximum aortic-to-pulmonary artery pressure gradient should be estimated. Cardiac catheterization is generally unnecessary for diagnosis, although it is important during interventional procedures. Catheterization findings include higher oxygen content in the pulmonary artery compared with the right ventricle (oxygen "step-up") and a wide aortic pressure pulse. Angiocardiography shows left-to-right shunting through the ductus (see Fig. 5-3, *C*).

# **Treatment and Prognosis**

Closure of the left-to-right ductus, usually performed as soon as is feasible, is recommended by either a transcatheter or surgical occlusion method. Surgical ligation is successful in most cases, although a perioperative mortality of about 10% has been reported. Patient age or weight does not appear to affect the outcome of surgery. Several methods of transcatheter PDA occlusion are available. These involve placing a vascular occluding device (e.g., the Amplatz canine ductal occluder) or wire coils with attached thrombogenic tufts within the ductus. Vascular access is usually via the femoral



TABLE 5-2

Radiographic Findings In Common Congenital Heart Defects

DEFECT	HEART	PULMONARY VESSELS	OTHER
PDA	LAE, LVE; left auricular bulge; ± increased cardiac width	Overcirculated	Bulge(s) in descending aorta + pulmonary trunk; ± pulmonary edema
SAS	± LAE, LVE	Normal	Wide cranial cardiac waist (dilated ascending aorta)
PS	RAE, RVE; reverse D	Normal to undercirculated	Pulmonary trunk bulge
VSD	LAE, LVE; ± RVE	Overcirculated	± Pulmonary edema; ± pulmonary trunk bulge (large shunts)
ASD	RAE, RVE	± Overcirculated	± Pulmonary trunk bulge
T dys	RAE, RVE; ± globoid shape	Normal	Caudal cava dilation; ± pleural effusion, ascites, hepatomegaly
M dys	LAE, LVE	± Venous hypertension	± Pulmonary edema
TofF	RVE, RAE; reverse D	Undercirculated; ± prominent bronchial vessels	Normal to small pulmonary trunk; ± cranial aortic bulge on lateral view
PRAA	Normal	Normal	Focal leftward and ventral tracheal deviation ± narrowing cranial to heart; wide cranial mediastinum; megaesophagus; (± aspiration pneumonia)

ASD, Atrial septal defect; LAE, left atrial enlargement; LVE, left ventricular enlargement; M dys, mitral dysplasia; PDA, patent ductus arteriosus; PS, pulmonic stenosis; RVE, right ventricular enlargement; RAE, right atrial enlargement; SAS, subaortic stenosis; T dys, tricuspid dysplasia; T of F, tetralogy of Fallot; VSD, ventricular septal defect.

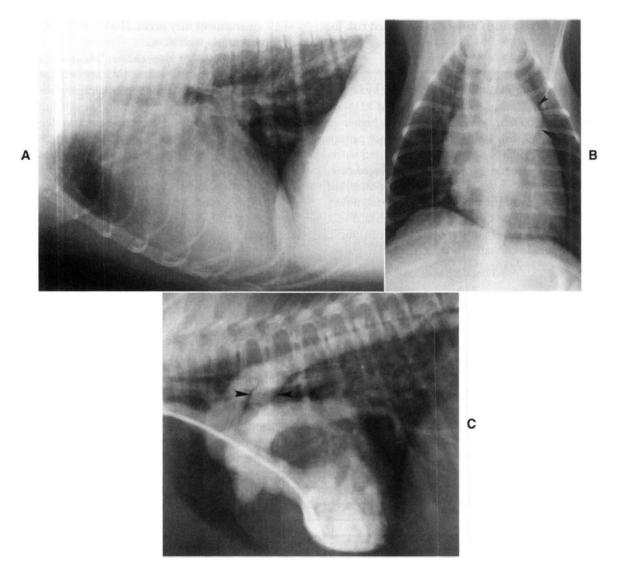


FIG 5-3
Lateral (A) and dorsoventral (DV) (B) radiographs from a dog with a patent ductus arteriosus. Note the large and elongated heart and prominent pulmonary vasculature. A large bulge is seen in the descending aorta on the DV view (arrowheads in B).

C, Angiocardiogram obtained using a left ventricular injection outlines the left ventricle, aorta, patent ductus (arrowheads), and pulmonary artery.

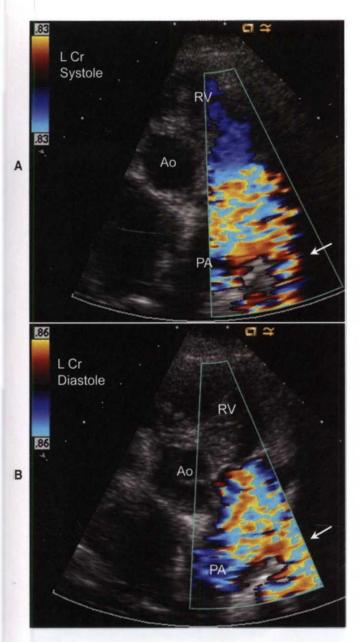
artery, although some have used a venous approach to the ductus. Where available, transcatheter PDA occlusion offers a much less invasive alternative to surgical ligation. Complications can occur (including aberrant coil embolization and residual ductal flow, among others), and not all cases are suitable for transcatheter occlusion. A normal life span can be expected after uncomplicated ductal closure. The concurrent mitral regurgitation usually resolves after ductus ligation or occlusion if the valve is structurally normal.

Animals with CHF are treated with furosemide, an angiotensin-converting enzyme inhibitor (ACEI), rest, and dietary sodium restriction (see Chapter 3). Because contractility tends to decline over time, pimobendan or digoxin may be indicated as well. Arrhythmias are treated as necessary.

If the ductus is not closed, prognosis depends on its size and the level of pulmonary vascular resistance. CHF is the eventual outcome for most patients that do not undergo ductal closure. More than 50% of affected dogs die within the first year. In animals with pulmonary hypertension and shunt reversal, ductal closure is contraindicated because the ductus acts as a "pop-off" valve for the high right-sided pressures. Ductal ligation in animals with reversed PDA produces no improvement and can lead to right ventricular (RV) failure.

# **VENTRICULAR OUTFLOW OBSTRUCTION**

Ventricular outflow obstruction can occur at the semilunar valve, just below the valve (subvalvular), or above the valve in the proximal great vessel (supravalvular). SAS and PS are most common in dogs and cats. Stenotic lesions impose a



Continuous turbulent flow into the pulmonary artery from the area of the patent ductus (arrow) is illustrated by systolic (A) and diastolic (B) color flow Doppler frames from the left cranial parasternal position, in an adult female Springer Spaniel. Ao, Ascending aorta; PA, main pulmonary artery; RV, right ventricle.

pressure overload on the affected ventricle, requiring higher systolic pressure as well as a slightly longer time to eject blood across the narrowed outlet. This generates a systolic pressure gradient across the stenosis because pressure downstream of the stenosis is normal. The magnitude of this gradient is related to the severity of the obstruction.

Concentric myocardial hypertrophy typically develops in response to a systolic pressure overload; some dilation of the affected ventricle can also occur. Ventricular hypertrophy can impede diastolic filling (by increasing ventricular stiffness) or lead to secondary AV valve regurgitation. Heart failure results when ventricular diastolic and atrial pressures are elevated. Cardiac arrhythmias can contribute to the onset of CHF. Furthermore, the combination of outflow obstruction, paroxysmal arrhythmias, and/or inappropriate bradycardia reflexly triggered by ventricular baroreceptor stimulation can result in signs of low cardiac output. These are often associated with severe outflow tract obstruction and include exercise intolerance, syncope, and sudden death.

#### SUBAORTIC STENOSIS

# **Etiology and Pathophysiology**

Subvalvular narrowing caused by a fibrous or fibromuscular ring is the most common type of aortic stenosis in dogs. Certain larger breeds of dog are predisposed to this defect. SAS is thought to be inherited as an autosomal dominant trait with modifying genes that influence its phenotypic expression. SAS also occurs in cats; supravalvular lesions have been reported in this species as well.

The spectrum of SAS severity varies widely; three grades of SAS have been described in Newfoundland dogs. The mildest (grade I) is associated with no clinical signs or murmur and only subtle subaortic fibrous tissue ridging seen on postmortem examination. Moderate (grade II) SAS consists of mild clinical and hemodynamic evidence of the disease, with an incomplete fibrous ring below the aortic valve found at postmortem. Dogs with grade III SAS have severe disease and a complete fibrous ring around the outflow tract. Some cases have an elongated, tunnel-like obstruction. There may also be malformations of the mitral valve apparatus. Outflow tract narrowing and dynamic obstruction with or without a discrete subvalvular ridge have also been noted in Golden Retrievers. A component of dynamic LV outflow tract obstruction may be important in other dogs as well.

The obstructive lesion of SAS develops during the first several months of life, and there may be no audible murmur at an early age. In some dogs no murmur is detected until 1 to 2 years of age, and the obstruction may continue to worsen beyond that. Murmur intensity usually increases with exercise or excitement. Because of such factors, as well as the presence of physiologic murmurs in some animals, definitive diagnosis and genetic counseling to breeders can be difficult.

The severity of the stenosis determines the degree of LV pressure overload and resulting concentric hypertrophy. Coronary perfusion is easily compromised in animals with severe SAS and left ventricular hypertrophy. Capillary density may become inadequate as hypertrophy progresses, and high systolic wall tension with coronary narrowing can cause systolic flow to be reversed in small coronary arteries. These factors contribute to the development of myocardial ischemia and fibrosis. Clinical sequelae include arrhythmias, syncope, and sudden death. Many animals with SAS also have aortic or mitral valve regurgitation because of related malformations or secondary changes; this imposes a volume overload on the LV. Left-sided CHF develops in some cases. Animals with SAS are thought to be at higher risk for devel-

oping aortic valve endocarditis because of jet lesion injury to the underside of the valve (see p. 121 and Figure 6-4).

#### **Clinical Features**

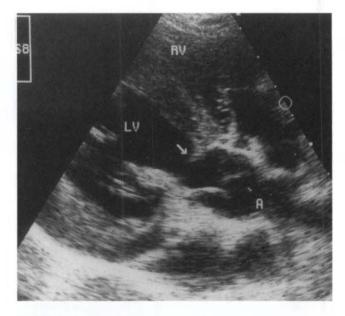
Historical signs of fatigue, exercise intolerance or exertional weakness, syncope, or sudden death occur in about a third of dogs with SAS. Low-output signs can result from severe outflow obstruction, tachyarrhythmias or sudden reflex bradycardia, and hypotension resulting from the activation of ventricular mechanoreceptors. Left-sided CHF can develop, usually in conjunction with concurrent mitral or aortic regurgitation, other cardiac malformations, or acquired endocarditis. Dyspnea is the most commonly reported sign in cats with SAS.

Characteristic physical examination findings in dogs with moderate-to-severe stenosis include weak and late-rising femoral pulses (pulsus parvus et tardus) and a precordial thrill low at the left heartbase. A harsh systolic ejection murmur is heard at or below the aortic valve area on the left hemithorax. This murmur often radiates equally or more loudly to the right heartbase because of the orientation of the aortic arch. The murmur frequently is heard over the carotid arteries, and it may even radiate to the calvarium. In mild cases a soft, poorly radiating ejection murmur at the left and sometimes right heartbase may be the only abnormality found on physical examination. Functional aortic stenosis murmurs that are not associated with SAS are common in Greyhounds and other sight hounds. Aortic regurgitation can produce a diastolic murmur at the left base or may be inaudible. Severe aortic regurgitation can increase the arterial pulse strength. There may be evidence of pulmonary edema or arrhythmias.

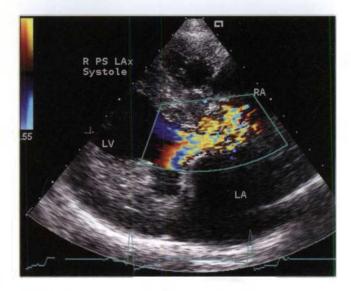
# **Diagnosis**

Radiographic abnormalities (see Table 5-2) can be subtle, especially in dogs and cats with mild SAS. The LV can appear normal or enlarged. Poststenotic dilation in the ascending aorta can cause a prominent cranial waist in the cardiac silhouette (especially on a lateral view) and cranial mediastinal widening. The ECG is often normal, although evidence of LV hypertrophy (left axis deviation) or enlargement (tall complexes) can be present. Depression of the ST segment in leads II and aVF can occur from secondary myocardial ischemia or to hypertrophy; exercise induces further ischemic ST-segment changes in some animals. Ventricular tachyarrhythmias are common.

Echocardiography reveals the extent of LV hypertrophy and subaortic narrowing. A discrete tissue ridge below the aortic valve is evident in many animals with moderate-to-severe disease (Fig. 5-5). Premature closure of the aortic valve, systolic anterior motion of the anterior mitral leaflet, and increased LV subendocardial echogenicity (probably from fibrosis) are common in animals with severe obstruction. Ascending aorta dilation, aortic valve thickening, and LA enlargement with hypertrophy may also be seen. In mildly affected animals 2-D and M-mode findings may be unremarkable. Doppler echocardiography reveals systolic



Echocardiogram from a 6-month-old German Shepherd Dog with severe subaortic stenosis. Note the discrete ridge of tissue (arrow) below the aortic valve, creating a fixed outflow tract obstruction. A, Aorta; LV, left ventricle; RV, right ventricle.



Color flow Doppler frame of the left ventricular outflow region in systole from a 2-year-old female Rottweiler with severe subaortic stenosis. Note the turbulent flow pattern originating below the aortic valve, as well as the thickened septum, papillary muscle, and left ventricular free wall. Right parasternal long axis view; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium.

turbulence originating below the aortic valve and extending into the aorta, as well as high peak systolic outflow velocity (Fig. 5-6). Some degree of aortic or mitral regurgitation is common. Spectral Doppler studies are used to estimate the stenosis severity. Doppler-estimated systolic pressure gradients in unanesthetized animals are usually 40% to 50%

higher than those recorded during cardiac catheterization under anesthesia. Severe SAS is associated with peak estimated gradients >100 to 125 mm Hg. The LV outflow tract should be interrogated from more than one position to achieve the best possible alignment with blood flow. The subcostal (subxiphoid) position usually yields the highestvelocity signals, although the left apical position is optimal in some animals. The Doppler-estimated aortic outflow velocity may be only equivocally high in animals with mild SAS, especially with suboptimal Doppler beam alignment. With optimal alignment, aortic root velocities of <1.7 m/sec are typical in normal unsedated dogs; velocities over ~2.25 m/ sec are generally considered abnormal. Peak velocities in the equivocal range between these values may indicate the presence of mild SAS, especially if there is other evidence of disease, such as disturbed flow in the outflow tract or ascending aorta and aortic regurgitation. This is mainly of concern when selecting animals for breeding. In some breeds (e.g., Greyhound, Boxer, Golden Retriever), outflow velocities in this equivocal range (1.8-2.25 m/sec) are common. This may reflect breed-specific variation in LV outflow tract anatomy or response to sympathetic stimulation, rather than SAS. A limitation of using the estimated pressure gradient to assess outflow obstruction severity is that this gradient depends on blood flow. Factors causing sympathetic stimulation and increased cardiac output (e.g., excitement, exercise, fever) will increase outflow velocities, whereas myocardial failure, cardiodepressant drugs, and other causes of reduced stroke volume will decrease recorded velocities. Cardiac catheterization and angiocardiography are rarely used now to diagnose or quantify SAS, except in conjunction with balloon dilation of the stenotic area.

# Treatment and Prognosis

Several palliative surgical techniques have been used in dogs with severe SAS, with limited success. Cardiopulmonary bypass and open-heart surgery are necessary to reach the lesion directly. Although resection of the stenotic area can significantly reduce the LV systolic pressure gradient and possibly improve exercise ability, a long-term survival advantage appears lacking. Transvascular balloon dilation of the stenotic area reduces the measured gradient in some dogs, although narrowing may partially recur. Likewise, no survival benefit has been documented with this procedure.

Medical therapy with a  $\beta$ -blocker is advocated in patients with moderate to severe SAS to reduce myocardial oxygen demand and minimize the frequency and severity of arrhythmias. Animals with a high pressure gradient, marked ST-segment depression, frequent ventricular premature beats, or a history of syncope may be more likely to benefit from this therapy. Whether  $\beta$ -blockers prolong survival is unclear. Exercise restriction is advised for animals with moderate-to-severe SAS. Prophylactic antibiotic therapy is recommended for animals with SAS before the performance of any procedures with the potential to cause bacteremia (e.g., dentistry).

The prognosis in dogs and cats with severe stenosis (catheterization pressure gradient >80 mm Hg or Doppler gradi-

ent >100-125 mm Hg) is guarded. More than half of dogs with severe SAS die suddenly within their first 3 years. The overall prevalence of sudden death in dogs with SAS appears to be just over 20%. Infective endocarditis and CHF may be more likely to develop after 3 years of age. Atrial and ventricular arrhythmias and worsened mitral regurgitation are complicating factors. Dogs with mild stenosis (e.g., catheterization gradient <35 mm Hg or Doppler gradient <60-70 mm Hg) are more likely to survive longer and without clinical signs.

#### **PULMONIC STENOSIS**

# **Etiology and Pathophysiology**

PS is more common in small breeds of dogs. Some cases of valvular PS result from simple fusion of the valve cusps, but valve dysplasia is more common. Dysplastic valve leaflets are variably thickened, asymmetric, and partially fused, with a hypoplastic valve annulus. Right ventricular pressure overload produces right ventricle (RV) hypertrophy as well as secondary dilation. Severe ventricular hypertrophy promotes myocardial ischemia and its sequelae. Excessive muscular hypertrophy below the valve (infundibular area) can create a dynamic subvalvular component to the stenosis. Other variants of PS, including supravalvular stenosis and RV muscular partition (double chamber RV) occur rarely.

High-velocity blood flow across the stenotic orifice creates turbulence leading to poststenotic dilation in the main pulmonary trunk. Right atrial dilation from secondary tricuspid insufficiency and high RV filling pressure predisposes to atrial tachyarrhythmias and CHF. The combination of PS and a patent foramen ovale or ASD can allow right-to-left shunting at the atrial level, but this is rare in dogs and cats.

A single anomalous coronary artery has been described in some Bulldogs and Boxers with PS and is thought to contribute to the outflow obstruction. In such cases, palliative surgical procedures and balloon valvuloplasty may cause death secondary to transection or avulsion of the major left coronary branch.

#### **Clinical Features**

Many dogs with PS are asymptomatic when diagnosed, although right-sided CHF or a history of exercise intolerance or syncope may exist. Clinical signs may not develop until the animal is several years old, even in those with severe stenosis. Physical examination findings characteristic of moderate-to-severe stenosis include a prominent right precordial impulse; a thrill high at the left base; normal to slightly diminished femoral pulses; pink mucous membranes; and, in some cases, jugular pulses. A systolic ejection murmur is heard best high at the left base on auscultation. The murmur can radiate cranioventrally and to the right in some cases but usually is not heard over the carotid arteries. An early systolic click is sometimes identified; this probably is caused by abrupt checking of a fused valve at the onset of ejection. A murmur of tricuspid insufficiency or arrhythmias can be heard in some cases.

# **Diagnosis**

Radiographic findings typically seen in animals with PS are outlined in Table 5-2. Marked RV hypertrophy shifts the cardiac apex dorsally and to the left. The heart may appear as a "reverse D" shape on a DV or ventrodorsal (VD) view. A variably sized pulmonary trunk bulge (poststenotic dilation) is best seen at the 1 o'clock position on a DV or VD view (Fig. 5-7). The size of the poststenotic dilation does not correlate with the severity of the pressure gradient. A dilated caudal vena cava is also seen in some animals.

ECG changes are more common in patients with moderate to severe stenosis. These include an RV hypertrophy pattern, right axis deviation, and sometimes an RA enlargement pattern (P pulmonale) or tachyarrhythmias. Echocar-

diographic findings characteristic of moderate-to-severe stenosis include RV hypertrophy and enlargement. The interventricular septum often appears flattened as high RV pressure pushes it toward the left (Figure 5-8, A). RA enlargement is often seen as well. A thickened, asymmetrical, or otherwise malformed pulmonic valve usually can be identified (Fig. 5-8, B), although the outflow area may be narrow and difficult to visualize clearly. Poststenotic dilation of the main pulmonary trunk is expected. Pleural effusion and marked right heart dilation often accompany secondary CHF. Paradoxical septal motion is likely in such cases as well. Doppler evaluation along with anatomic findings provides an estimate of PS severity. Cardiac catheterization and angiocardiography also can be used to assess the pressure gradient

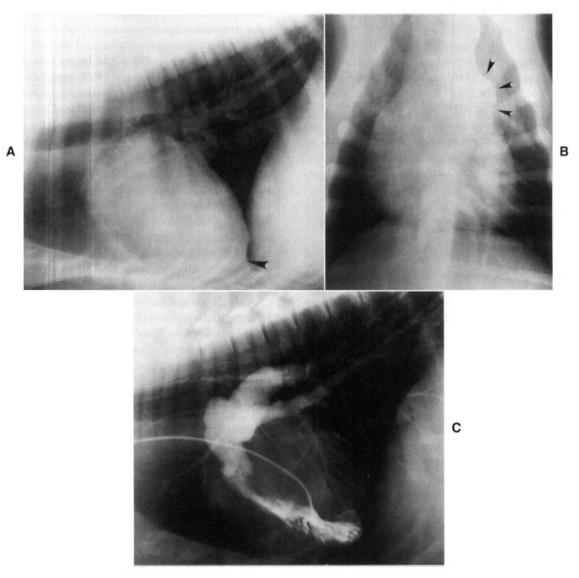
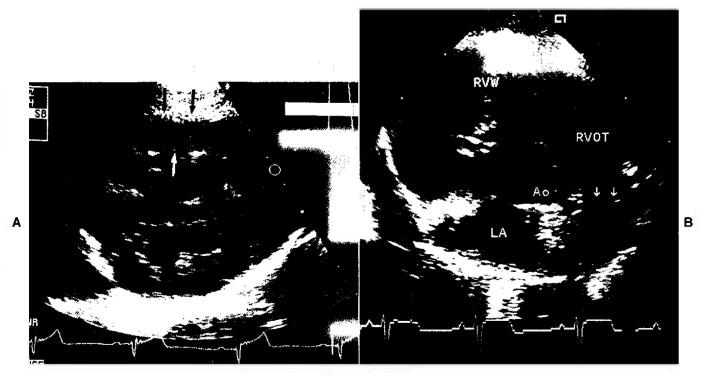


FIG 5-7
Lateral (A) and dorsoventral (DV) (B) radiographs from a dog with pulmonic stenosis, showing right ventricular enlargement (apex elevation on lateral view [arrowhead in A] and reverse D configuration on DV view) along with a pulmonary trunk bulge (arrowheads in B) seen on a DV view. C, Angiocardiogram using a selective right ventricular injection demonstrates poststenotic dilation of the main pulmonary trunk and pulmonary arteries. The thickened pulmonic valve is closed in this diastolic frame.



Echocardiograms from two dogs with severe pulmonic stenosis. (A) Right parasternal short-axis view at the ventricular level in a 4-month-old male Samoyed shows right ventricular hypertrophy (arrows) and enlargement; high right ventricular pressure flattens the septum toward the left in this diastolic frame. (B) Thickened, partially fused leaflets of the malformed pulmonary valve (arrows) are seen in a 5-month-old male Pomeranian. Ao, Aortic root; LA, left atrium; RVOT, right ventricular outflow tract; RVW, right ventricular wall.

across the stenotic valve, the right heart filling pressure, and other anatomic features. Doppler-estimated systolic pressure gradients in unanesthetized animals are usually 40% to 50% higher than those recorded during cardiac catheterization. PS is generally considered mild if the Doppler-derived gradient is <50 mm Hg and severe if it is >80 to 100 mm Hg.

# **Treatment and Prognosis**

Balloon valvuloplasty is recommended for palliation of severe (and sometimes moderate) stenosis, especially if infundibular hypertrophy is not excessive. This procedure reduces or eliminates clinical signs and appears to improve long-term survival in severely affected animals. Balloon valvuloplasty, done in conjunction with cardiac catheterization, involves passing a specially designed balloon catheter across the valve and inflating the balloon to enlarge the stenotic orifice. The procedure is most successful in dogs with simple fusion of the pulmonic valve cusps. Dysplastic valves are more difficult to dilate effectively, but good results are possible in some cases. Various surgical procedures also have been used to palliate moderate-to-severe PS in dogs. Balloon valvuloplasty generally is attempted before a surgical procedure because it is less risky. Animals with a single anomalous coronary artery should not undergo balloon or surgical dilation procedures. Coronary anatomy can be verified using echocardiography or angiography.

Exercise restriction is generally advised for animals with moderate-to-severe stenosis. A  $\beta$ -blocker may be helpful, especially in those with prominent RV infundibular hypertrophy. Signs of CHF are managed medically (see Chapter 3). The prognosis in patients with PS is variable and depends on the severity of the lesion. Life span can be normal in those with mild PS, whereas animals with severe PS often die within 3 years of diagnosis. Sudden death or the onset of CHF is common. The prognosis is considerably worse in animals with tricuspid regurgitation, atrial fibrillation or other tachyarrhythmias, or CHF.

# INTRACARDIAC SHUNT

Blood flow volume across an intracardiac shunt depends on the size of the defect and the pressure gradient across it. In most cases, flow direction is from left to right, causing pulmonary overcirculation. Compensatory increases in blood volume and cardiac output occur in response to the partial diversion of blood away from the systemic circulation. A volume overload is imposed on the side of the heart doing the most work. If right heart pressures increase as a result of pulmonary hypertension or a concurrent PS, shunt flow may equilibrate or reverse (i.e., become right-to-left).

#### **VENTRICULAR SEPTAL DEFECT**

# **Etiology and Pathophysiology**

Most VSDs are located in the membranous part of the septum, just below the aortic valve and beneath the septal tricuspid leaflet. VSDs sporadically occur in other septal locations also. A VSD may be accompanied by other AV septal (endocardial cushion) malformations, especially in cats. Usually, VSDs produce a volume overload on the lungs, LA, LV, and RV outflow tract. Small defects may be clinically unimportant. Moderate-to-large defects tend to cause left heart dilation and can lead to left-sided CHF. A very large VSD causes both ventricles to function as a common chamber and induces RV dilation and hypertrophy. Pulmonary hypertension secondary to overcirculation is more likely to develop in animals with a large shunt. Some animals with VSD also have aortic regurgitation, with diastolic prolapse of a valve leaflet. Presumably this occurs because the deformed septum provides inadequate anatomic support for the aortic root. Aortic regurgitation places an additional volume load on the LV.

#### **Clinical Features**

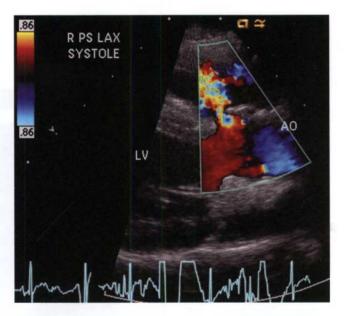
The most common clinical manifestations of VSD are exercise intolerance and signs of left-sided CHF. Many animals are asymptomatic at the time of diagnosis. The characteristic auscultatory finding is a holosystolic murmur, heard loudest at the cranial right sternal border (which corresponds to the direction of shunt flow). A large shunt volume can produce a murmur of relative or functional PS (systolic ejection murmur at the left base). With concurrent aortic regurgitation, the corresponding diastolic decrescendo murmur is heard at the left base.

# **Diagnosis**

Radiographic findings associated with VSD vary with thesize of the defect and the shunt volume (see Table 5-2). Large shunts cause left heart enlargement and pulmonary overcirculation. However, large shunts that increase pulmonary vascular resistance and pressure lead to RV enlargement. A large shunt volume (with or without pulmonary hypertension) also can increase main pulmonary trunk size.

The ECG may be normal or suggest LA or LV enlargement. In some cases, disturbed intraventricular conduction is suggested by "fractionated" or splintered QRS complexes. An RV enlargement pattern usually indicates a very large defect, pulmonary hypertension, or a concurrent RV outflow tract obstruction, although sometimes a right bundle-branch block causes this pattern.

Echocardiography reveals left heart dilation (with or without RV dilation) when the shunt is large. The defect often can be visualized just below the aortic valve in the right parasternal long-axis LV outflow view. The septal tricuspid leaflet is located to the right of the defect. Because echo "dropout" at the thin membranous septum can mimic a VSD, the area of a suspected defect should be visualized in



Color flow Doppler frame in systole showing turbulent flow (from left to right) through a small membranous ventricular septal defect just below the aortic root in a 1-year-old male terrier. Right parasternal long axis view; AO, aortic root; LV, left ventricle.

more than one plane. Supporting clinical evidence and a murmur typical of a VSD also should be present before the diagnosis is made. Doppler (or echo-contrast) studies usually demonstrate the shunt flow (Fig. 5-9).

Cardiac catheterization, oximetry, and angiocardiography allow measurement of intracardiac pressures, indicate the presence of an oxygen step-up at the level of the RV outflow tract, and show the pathway of abnormal blood flow.

# **Treatment and Prognosis**

A small-to-moderate defect usually allows a relatively normal life span. In some cases, the defect closes spontaneously within the first 2 years of life. Closure can result from myocardial hypertrophy around the VSD or a seal formed by the septal tricuspid leaflet or a prolapsed aortic leaflet. Left-sided CHF is more likely in animals with a large septal defect, although pulmonary hypertension with shunt reversal develops in some instead, usually at an early age.

Definitive therapy for VSD usually requires cardiopulmonary bypass or hypothermia and intracardiac surgery, although transcatheter delivery of an occlusion device may be possible in some cases. Large left-to-right shunts are sometimes palliated by surgically placing a constrictive band around the pulmonary trunk to create a mild supravalvular PS. This raises RV systolic pressure in response to the increased outflow resistance. Consequently, less blood shunts from LV to RV. An excessively tight band can cause right-to-left shunting (functionally analogous to a T of F), however. Left-sided CHF is managed medically. Palliative surgery

should not be attempted in the presence of pulmonary hypertension and shunt reversal.

# ATRIAL SEPTAL DEFECT

# **Etiology and Pathophysiology**

Several types of ASD exist. Those located in the region of the fossa ovalis (ostium secundum defects) are more common in dogs. An ASD in the lower interatrial septum (ostium primum defect) is likely to be part of the AV septal (endocardial cushion or common AV canal) defect complex, especially in cats. Sinus venosus—type defects are rare; these are located high in the atrial septum near the entry of the cranial vena cava. Animals with ASD commonly have other cardiac malformations as well. In most cases of ASD, blood shunts from LA to RA and results in a volume overload to the right heart. However, if PS or pulmonary hypertension is present, right-to-left shunting and cyanosis may occur.

# **Clinical Features**

The clinical history in animals with an ASD is usually rather nonspecific. Physical examination findings associated with an isolated ASD are often unremarkable, although large left-to-right shunts can cause a murmur of relative PS. Fixed splitting (i.e., with no respiratory variation) of the second heart sound  $(S_2)$  is the classic auscultatory finding. Rarely, a soft diastolic murmur of relative tricuspid stenosis might be audible.

# Diagnosis

Right heart enlargement, with or without pulmonary trunk dilation, is found radiographically in patients with severe shunts (see Table 5-2). The pulmonary circulation may appear to be increased unless pulmonary hypertension has developed. Left heart enlargement is not seen unless another defect, such as mitral insufficiency, is present. The ECG may be normal or show evidence of RV and RA enlargement. Cats with an AV septal defect may have RV enlargement and a left axis deviation.

Echocardiography is likely to show RA and RV dilation, with or without paradoxical interventricular septal motion. Large ASDs can be visualized. Care must be taken not to confuse the thinner fossa ovalis region of the interatrial septum with an ASD because echo dropout also occurs here. Doppler echocardiography allows identification of smaller shunts that cannot be clearly visualized on 2-D exam, but venous inflow streams may complicate this. Cardiac catheterization shows an oxygen step-up at the level of the RA. Abnormal flow through the shunt may be evident after the injection of contrast material into the pulmonary artery.

# **Treatment and Prognosis**

Large shunts can be treated surgically, similarly to VSDs. Otherwise, animals are managed medically if CHF develops. The prognosis is variable and depends on shunt size, concurrent defects, and the level of pulmonary vascular resistance.

# ATRIOVENTRICULAR VALVE MALFORMATION

# MITRAL DYSPLASIA

Congenital malformations of the mitral valve apparatus include shortened or overly elongated chordae tendineae, direct attachment of the valve cusp to a papillary muscle, thickened or cleft or shortened valve cusps, prolapse of valve leaflets, upwardly displaced or malformed papillary muscles, and excessive dilation of the valve annulus. Mitral valve dysplasia (MD) is most common in large-breed dogs and also occurs in cats. Valvular regurgitation is the predominant functional abnormality, and it may be severe; the pathophysiology and sequelae resemble those of acquired mitral regurgitation (see p. 121). Mitral valve stenosis is uncommon. Obstruction to ventricular filling increases LA pressure and can precipitate the development of pulmonary edema. Mitral regurgitation usually accompanies stenosis.

The clinical signs seen in patients with MD are similar to those in dogs with degenerative mitral valve disease, except for the younger patient age. Reduced exercise tolerance, respiratory signs of left-sided CHF, inappetence, and atrial arrhythmias (especially atrial fibrillation) are common in affected animals. Mitral regurgitation typically causes a systolic murmur heard best at the left apex.

The radiographic, ECG, echocardiographic, and catheterization findings are similar to those found in patients with acquired mitral insufficiency. Echocardiography can depict the specific mitral apparatus malformations as well as the degree of chamber enlargement and functional changes.

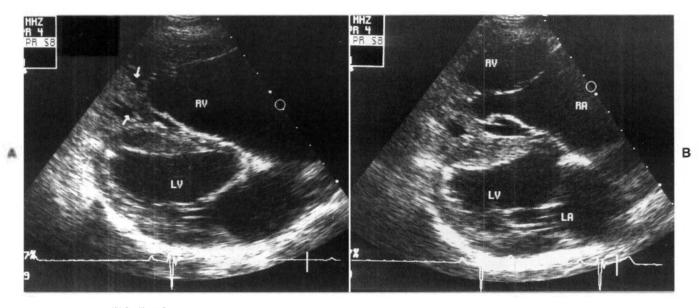
Therapy consists of medical management for CHF. Animals with mild to moderate mitral valve dysfunction may do well clinically for years. However, for those with severe mitral regurgitation or stenosis, the prognosis is poor. Surgical valve reconstruction or replacement may be possible in some cases.

#### TRICUSPID DYSPLASIA

Animals with tricuspid dysplasia (TD) have malformations of the tricuspid valve and related structures that are similar to those of MD. The tricuspid valve can be displaced ventrally into the ventricle (an Ebsteinlike anomaly) in some cases; ventricular preexcitation may be more likely in these animals. Tricuspid dysplasia is identified most frequently in large-breed dogs, particularly in Labrador Retrievers, and in males.

The pathophysiologic features of TD are the same as those of acquired tricuspid regurgitation. Severe cases result in marked enlargement of the right heart chambers. Progressive increase in RA and RV end-diastolic pressures eventually result in right-sided CHF. Tricuspid stenosis is rare.

The historical signs and clinical findings likewise are similar to those of degenerative tricuspid disease. Initially, the animal may be asymptomatic or mildly exercise intolerant. However, exercise intolerance, abdominal distention resulting from ascites, dyspnea resulting from pleural effusion, anorexia, and cardiac cachexia often develop. The



Right parasternal long-axis echo images from a 1-year-old male Labrador Retriever with tricuspid valve dysplasia in diastole (**A**) and systole (**B**). The valve annulus appears to be ventrally displaced; the leaflet tips are tethered to a malformed, wide papillary muscle (arrows in **A**). Wide leaflet tip separation in systole (**B**) caused severe tricuspid regurgitation and clinical congestive heart failure. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

murmur of tricuspid regurgitation is characteristic but not always clearly audible. Jugular pulsations are common. Additional signs that accompany CHF include jugular vein distention, muffled heart and lung sounds, and ballotable abdominal fluid.

Radiographs demonstrate RA and RV enlargement. The round appearance of the heart shadow in some cases is similar to that seen in patients with pericardial effusion or dilated cardiomyopathy. A distended caudal vena cava, pleural or peritoneal effusion, and hepatomegaly are common.

RV and occasionally RA enlargement patterns are seen on ECG. A splintered QRS complex configuration may be seen. Atrial fibrillation or another atrial tachyarrhythmias occur commonly. Some patients exhibit signs of ventricular preexcitation.

Echocardiography reveals right heart dilation, which can be massive. Valve apparatus malformations also may be clear in several views (Fig. 5-10), although the left apical four-chamber view is especially useful. Intracardiac electrocardiography is necessary to confirm an Ebstein's anomaly, which is suggested by ventral displacement of the tricuspid valve annulus. A ventricular electrogram recorded on the RA side of the valve is diagnostic, although this technique is rarely done in the clinic.

CHF and arrhythmias are managed medically. Periodic thoracocentesis may be needed in animals with pleural effusion that cannot be controlled with medication and diet. The prognosis is guarded to poor, especially when cardiomegaly is marked. Nevertheless, some dogs survive for several years. Balloon dilation has been used successfully to treat tricuspid stenosis.

# CARDIAC ANOMALIES CAUSING CYANOSIS

Malformations that allow deoxygenated blood to reach the systemic circulation result in hypoxemia. Visible cyanosis occurs when the desaturated hemoglobin concentration is >5 g/dl. Arterial hypoxemia stimulates increased red blood cell production, which increases oxygen carrying capacity. However, blood viscosity and resistance to flow also rise with the increase in PCV. Severe erythrocytosis (PCV >65%) can lead to microvascular sludging, poor tissue oxygenation, intravascular thrombosis, hemorrhage, stroke, and cardiac arrhythmias. Erythrocytosis can become extreme, with a PCV >80% in some animals. The possibility of a venous embolus crossing the shunt to the systemic circulation poses another danger in these cases.

Anomalies that most often cause cyanosis in dogs and cats are T of F and pulmonary arterial hypertension secondary to a large PDA, VSD, or ASD. Other complex but uncommon anomalies, such as transposition of the great vessels or truncus arteriosus, also send deoxygenated blood to the systemic circulation. Some collateral blood flow to the lungs develops from the bronchial arteries of the systemic circulation. These small tortuous vessels may increase the overall radiographic opacity of the central pulmonary fields.

Physical exertion tends to exacerbate right-to-left shunting and cyanosis because greater blood flow to skeletal muscle reduces total peripheral vascular resistance. Despite the pressure overload on the right heart, CHF is rare. The shunt provides an alternate pathway for high pressure flow.

# TETRALOGY OF FALLOT

# **Etiology and Pathophysiology**

The four components of the T of F are a VSD, PS, a dextropositioned aorta, and RV hypertrophy. The VSD can be quite large. The PS can involve the valve or infundibular area; in some cases, the pulmonary artery is hypoplastic or not open at all (atretic). The large aortic root extends over the right side of the interventricular septum and facilitates RV-toaortic shunting. Aortic anomalies exist in some animals as well. RV hypertrophy occurs in response to the pressure overload imposed by the PS and systemic arterial circulation. The volume of blood shunted from the RV into the aorta depends on the balance of outflow resistance caused by the fixed PS compared with systemic arterial resistance, which can vary. Exercise and other causes of decreased arterial resistance increase right-to-left shunt volume. Pulmonary vascular resistance is generally normal in animals with T of F. A polygenic inheritance pattern for T of F has been identified in the Keeshond. The defect also occurs in other dog breeds and in cats.

# **Clinical Features**

Exertional weakness, dyspnea, syncope, cyanosis, and stunted growth are common in the history. Physical examination findings are variable, depending on the relative severity of the malformations. Cyanosis is seen at rest in some animals. Others have pink mucous membranes, although cyanosis usually becomes evident with exercise in these cases. The precordial impulse is usually of equal intensity or stronger on the right chest wall than on the left. Inconsistently, a precordial thrill is palpable at the right sternal border or left basilar area. Jugular pulsation may be noted. A holosystolic murmur at the right sternal border consistent with a VSD, or a systolic ejection murmur at the left base compatible with PS, or both may be heard on auscultation. However, some animals have no audible murmur because hyperviscosity associated with polycythemia diminishes blood turbulence and therefore murmur intensity.

#### Diagnosis

Thoracic radiographs depict variable cardiomegaly, usually of the right heart (see Table 5-2). The main pulmonary artery may appear small, although a bulge is evident in some cases. Reduced pulmonary vascular markings are common, although a compensatory increase in bronchial circulation can increase the overall pulmonary opacity. The malpositioned aorta creates a cranial bulge in the heart shadow on lateral view. RV hypertrophy displaces the left heart dorsally and can simulate left heart enlargement. The ECG typically suggests RV enlargement, although a left axis deviation is seen in some affected cats.

Echocardiography depicts the VSD, a large aortic root shifted rightward and overriding the ventricular septum, some degree of PS, and RV hypertrophy. Doppler studies reveal the right-to-left shunt and high-velocity stenotic pulmonary outflow jet. An echo-contrast study also can

document the right-to-left shunt. Typical clinicopathologic abnormalities include increased PCV and arterial hypoxemia.

# **Treatment and Prognosis**

Definitive repair of T of F requires open-heart surgery. Palliative surgical procedures can increase pulmonary blood flow by creating a left-to-right shunt. Anastomosis of a subclavian artery to the pulmonary artery and the creation of a window between the ascending aorta and pulmonary artery are two techniques that have been used successfully.

Severe erythrocytosis and clinical signs associated with hyperviscosity (e.g., weakness, shortness of breath, seizures) can be treated with periodic phlebotomy (see p. 111) or alternatively, hydroxyurea (see p. 111). The goal is to maintain PCV at a level where clinical signs are minimal; further reduction of PCV (into the normal range) can exacerbate signs of hypoxia. A  $\beta$ -blocker may help reduce clinical signs in some dogs with T of F. Decreased sympathetic tone, RV contractility, RV (muscular) outflow obstruction, and myocardial oxygen consumption, along with increased peripheral vascular resistance, are potential benefits, although the exact mechanism is not clear. Exercise restriction is also advised. Drugs with systemic vasodilator effects should not be given.

The prognosis for animals with T of F depends on the severity of PS and erythrocytosis. Mildly affected animals and those that have had a successful palliative surgical shunting procedure may survive well into middle age. Nevertheless, progressive hypoxemia, erythrocytosis, and sudden death at an earlier age are common.

# PULMONARY HYPERTENSION WITH SHUNT REVERSAL

# **Etiology and Pathophysiology**

Pulmonary hypertension develops in a relatively small percentage of dogs and cats with shunts. The defects usually associated with development of pulmonary hypertension are PDA, VSD, AV septal defect or common AV canal, ASD, and aorticopulmonary window. The low-resistance pulmonary vascular system normally can accept a large increase in blood flow without marked increase in pulmonary arterial pressure. It is not clear why pulmonary hypertension develops in some animals, although the defect size in those animals is usually quite large. It is possible that the high fetal pulmonary resistance may not regress normally in these animals or their pulmonary vasculature may react abnormally to an initially large left-to-right shunt flow. In any case, irreversible histologic changes occur in the pulmonary arteries that increase vascular resistance. These include intimal thickening, medial hypertrophy, and characteristic plexiform lesions.

As pulmonary vascular resistance rises, pulmonary artery pressure increases and the volume of blood shunted from left-to-right diminishes. If the right heart and pulmonary pressures exceed those of the systemic circulation, the shunt reverses direction and deoxygenated blood flows into the

aorta. These changes appear to develop at an early age (e.g., by 6 months), although exceptions are possible. The term *Eisenmenger's physiology* refers to the severe pulmonary hypertension and shunt reversal that develop.

Right-to-left shunts that result from pulmonary hypertension cause pathophysiologic and clinical sequelae similar to those resulting from T of F. The major difference is that the impediment to pulmonary flow occurs at the level of the pulmonary arterioles rather than at the pulmonic valve. Hypoxemia, RV hypertrophy and enlargement, erythrocytosis and its consequences, increased shunting with exercise, and cyanosis can occur. Likewise, right-sided CHF is uncommon but can develop in response to secondary myocardial failure or tricuspid insufficiency. The right-to-left shunt permits venous emboli to cross into the arterial system, potentially resulting in stroke or other arterial embolization.

#### **Clinical Features**

The history and clinical presentation of animals with pulmonary hypertension and shunt reversal are similar to those associated with T of F. Exercise intolerance, shortness of breath, syncope (especially in association with exercise or excitement), seizures, and sudden death are common. Cough and hemoptysis may also occur. Cyanosis may be evident

only during exercise or excitement. Intracardiac shunts cause equally intense cyanosis throughout the body. Cyanosis of the caudal mucous membranes alone (differential cyanosis) is typically caused by a reversed PDA. Here, normally oxygenated blood flows to the cranial body by way of the brachycephalic trunk and left subclavian artery (from the aortic arch), and the rest of the body receives desaturated blood through the ductus, located in the descending aorta (Fig. 5-11). Rear limb weakness is common in animals with reversed PDA.

A murmur typical of the underlying defect(s) may be heard, but often no murmur or only a very soft systolic murmur is audible because blood viscosity is increased by polycythemia. There is no continuous murmur in patients with reversed PDA. Pulmonary hypertension often causes the S<sub>2</sub> sound to be loud and "snapping" or split. A gallop sound is occasionally heard. Other subtle physical examination findings include a pronounced right precordial impulse and jugular pulsations.

# Diagnosis

Thoracic radiographs typically reveal right heart enlargement; a prominent pulmonary trunk; and tortuous, proximally widened pulmonary arteries. A bulge in the descending

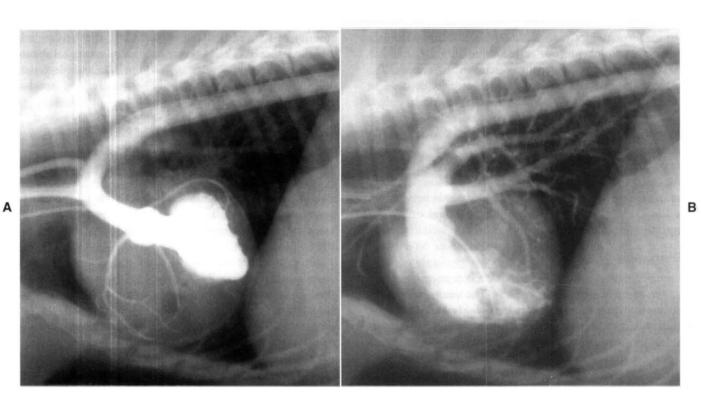


FIG 5-11

Angiocardiograms from an 8-month-old female Cocker Spaniel with patent ductus arteriosus, pulmonary hypertension, and shunt reversal. Left ventricular injection (A) shows dorsal displacement of the left ventricle by the enlarged right ventricle. Note the dilution of radiographic contrast solution in the descending aorta (from mixing with nonopacified blood from the ductus) and the prominent right coronary artery. Right ventricular injection (B) illustrates right ventricular hypertrophy and pulmonary trunk dilation secondary to severe pulmonary hypertension. Opacified blood courses through the large ductus into the descending aorta.

aorta may be seen in dogs with reversed PDA. The left heart in animals with a reversed PDA or VSD may be enlarged as well. The ECG usually suggests RV and sometimes RA enlargement, with a right axis deviation.

Echocardiography reveals the RV hypertrophy and intracardiac anatomic defects (and sometimes a large ductus), as well as pulmonary trunk dilation. Doppler or echo-contrast study can confirm an intracardiac right-to-left shunt. Reversed PDA flow can be shown by imaging the abdominal aorta during venous echocontrast injection. Peak RV (and in the absence of PS, pulmonary artery) pressure can be estimated by measuring the peak velocity of a tricuspid regurgitation jet. Pulmonary insufficiency flow can be used to estimate diastolic pulmonary artery pressure. Cardiac catheterization also can confirm the diagnosis and quantify the pulmonary hypertension and systemic hypoxemia.

# **Treatment and Prognosis**

Therapy is aimed at managing secondary erythrocytosis to minimize signs of hyperviscosity and attempting to reduce pulmonary arterial pressure, if possible. Exercise restriction is also advised. Erythrocytosis can be managed by periodic phlebotomy or use of oral hydroxyurea. It is unclear whether PCV alone should be used to guide treatment, although maintaining PCV at about 62% has previously been recommended. The ideal PCV for a patient would seem to be that associated with minimal physical manifestations of hyperviscosity (e.g., rear limb weakness, shortness of breath, lethargy). Surgical closure of the shunt is contraindicated. The prognosis is generally poor in animals with pulmonary hypertension and shunt reversal, but some patients have done well for years with medical management.

Phlebotomy can be done when necessary. One method is to remove 5 to 10 ml blood/kg body weight and administer an equal volume of isotonic fluid. Another technique (described by Cote and Ettinger, 2001) involves removing 10% of the patient's circulating blood volume initially without giving replacement fluid. This volume (ml) is calculated as  $8.5\% \times \text{body}$  weight (kg)  $\times 1000 \text{ g/kg} \times 1 \text{ ml/g}$ . After 3 to 6 hours of cage rest, an additional volume of blood is removed if the patient's initial PCV was >60%. This additional volume would be 5% to 10% of the circulating blood volume if initial PCV was 60% to 70%, or an additional 10% to 18% if initial PCV was >70%.

Hydroxyurea therapy (40 to 50 mg/kg by mouth q48h or 3×/week) can be a useful alternative to periodic phlebotomy in some patients with secondary erythrocytosis. A CBC and platelet count should be monitored weekly or biweekly to start. A PCV between approximately 55% to 60% is the suggested target. Possible adverse effects of hydroxyurea include anorexia, vomiting, bone marrow hypoplasia, alopecia, and pruritus. The dose can be divided q12h on treatment days, or administered twice weekly, or at <40 mg/kg depending on the patient's response.

Sildenafil citrate is a selective phosphodiesterase-5 inhibitor that may reduce pulmonary resistance via nitric oxide—dependent pulmonary vasodilation. It appears to improve

clinical signs and exercise tolerance in some dogs with pulmonary hypertension, although experience in animals is limited. Doses of 0.5 to 2(or 3) mg/kg q12h or q8h seem to be well-tolerated and produce some reduction in Doppler-cstimated pulmonary artery pressure. Lower initial doses are suggested, with gradual up-titration. Adverse effects of sildenafil can include possible nasal congestion, hypotension, or sexual adverse effects, especially in intact animals. Other vasodilator drugs tend to produce systemic effects that are similar to or greater than those on the pulmonary vasculature; therefore they are of little benefit and possibly detrimental. Low-dose aspirin (e.g., 5 mg/kg) therapy may also be useful in animals with pulmonary hypertension and reversed shunt, but this is not well-studied.

# OTHER CARDIOVASCULAR ANOMALIES

# **VASCULAR RING ANOMALIES**

Various vascular malformations originating from the embryonic aortic arch system can occur. These can entrap the esophagus and sometimes the trachea within a vascular ring at the dorsal heart base. Persistent right aortic arch is the most common vascular ring anomaly in the dog. This developmental malformation surrounds the esophagus: dorsally and to the right with the aortic arch, to the left with the ligamentum arteriosum, and ventrally with the base of the heart. Different vascular ring anomalies can occur as well. In addition, other vascular malformations, such as a left cranial vena cava or PDA, may accompany a vascular ring anomaly. Vascular ring anomalies are rare in cats.

The vascular ring prevents solid food from passing normally through the esophagus. Clinical signs of regurgitation and stunted growth commonly develop within 6 months of weaning. Esophageal dilation occurs cranial to the ring; food may be retained in this area. Sometimes the esophagus dilates caudal to the stricture as well, indicating that altered esophageal motility coexists. Respiratory signs including coughing, wheezing, and cyanosis usually signal secondary aspiration pneumonia. However, in some cases a double aortic arch can cause stridor and other respiratory signs secondary to tracheal stenosis.

The animal's body condition score may be normal initially, but progressive debilitation ensues. A palpably dilated cervical esophagus (containing food or gas) is evident at the thoracic inlet in some cases. Fever and respiratory signs suggest aspiration pneumonia. Vascular ring anomalies by themselves do not result in abnormal cardiac sounds.

Thoracic radiographs show a leftward tracheal deviation near the cranial heart border on DV view. Other common signs include a widened cranial mediastinum, focal narrowing and/or ventral displacement of the trachea, air or food in the cranial thoracic esophagus, and sometimes evidence of aspiration pneumonia. A barium swallow allows visualization of the esophageal stricture over the heartbase and cranial esophageal dilation (with or without caudal esophageal dilation).

Surgical division of the ligamentum arteriosum, or other vessel if the anomaly is not a persistent right aortic arch, is the recommended therapy. In some cases a retroesophageal left subclavian artery or left aortic arch is also present and must be divided to free the esophagus. Medical management consists of frequent small, semisolid, or liquid meals eaten in an upright position. This feeding method may be necessary indefinitely. Persistent regurgitation occurs in some dogs despite successful surgery, suggesting a permanent esophageal motility disorder.

# COR TRIATRIATUM

Cor triatriatum is an uncommon malformation caused by an abnormal membrane that divides either the right (dexter) or the left (sinister) atrium into two chambers. Cor triatriatum dexter occurs sporadically in dogs; cor triatriatum sinister has been described only rarely. Cor triatriatum dexter results from failure of the embryonic right sinus venosus valve to regress. The caudal vena cava and coronary sinus empty into the RA caudal to the intra-atrial membrane; the tricuspid orifice is within the cranial RA "chamber." Obstruction to venous flow through the opening in the abnormal membrane elevates vascular pressure in the caudal vena cava and the structures that drain into it.

Large- to medium-size breeds of dog are most often affected. Persistent ascites that develops at an early age is the most prominent clinical sign. Exercise intolerance, lethargy, distended cutaneous abdominal veins, and sometimes diarrhea are reported also. Neither a cardiac murmur nor jugular venous distention are features of this anomaly.

Thoracic radiographs indicate caudal vena caval distention without generalized cardiomegaly. The diaphragm may be displaced cranially by massive ascites. The ECG is usually normal. Echocardiography reveals the abnormal membrane and prominence of the caudal RA chamber and vena cava. Doppler studies show the flow disturbance within the RA and allow the intra-RA pressure gradient to be estimated.

Successful therapy requires enlarging the membrane orifice or excising the abnormal membrane to remove flow obstruction. A surgical approach using inflow occlusion, with or without hypothermia, can be used to excise the membrane or break it down using a valve dilator. A much less invasive option is percutaneous balloon dilation of the membrane orifice. This works well as long as a sufficiently large balloon is used. Several balloon dilation catheters placed simultaneously may be needed for effective dilation in larger dogs.

#### **ENDOCARDIAL FIBROELASTOSIS**

Diffuse fibrosis and elastic thickening of the endocardium characterize the congenital abnormality endocardial fibroelastosis. It is reported more commonly in cats, especially Burmese and Siamese, but has been observed rarely in dogs. Left-sided or biventricular heart failure commonly develops early in life. A mitral regurgitation murmur may be present. Criteria for LV and LA enlargement are seen on radiographs, ECG, and echocardiogram. Evidence for reduced LV myo-

cardial systolic and diastolic function may be present. Definitive antemortem diagnosis is difficult.

#### **OTHER VASCULAR ANOMALIES**

A number of venous anomalies have been described. Many are not clinically important. The persistent left cranial vena cava is a fetal venous remnant that courses lateral to the left AV groove and empties into the coronary sinus of the caudal RA. Although it causes no clinical signs, its presence may complicate surgical exposure of other structures at the left heartbase. Portosystemic venous shunts are common and can lead to hepatic encephalopathy as well as other signs. These malformations are thought to be more prevalent in the Yorkshire Terrier, Pug, Miniature and Standard Schnauzers, Maltese, Pekingese, Shih Tzu, and Lhasa Apso breeds.

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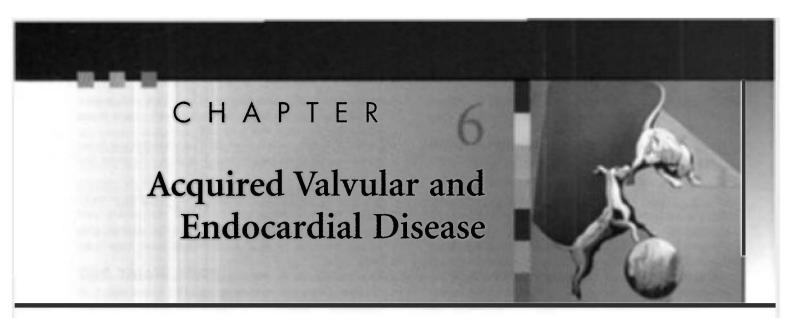
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# CHAPTER OUTLINE

DEGENERATIVE ATRIOVENTRICULAR VALVE DISEASE Radiography Electrocardiography Echocardiography INFECTIVE ENDOCARDITIS

# DEGENERATIVE ATRIOVENTRICULAR VALVE DISEASE

Chronic degenerative atrioventricular (AV) valve disease is the most common cause of heart failure in the dog. This condition is also known as endocardiosis, mucoid or myxomatous valvular degeneration, or chronic valvular fibrosis. Because clinically relevant degenerative valve disease is rare in cats, this chapter will focus on canine chronic valvular disease. The mitral valve is affected most often and to a greater degree, but degenerative lesions also involve the tricuspid valve in many dogs. However, isolated degenerative disease of the tricuspid valve is uncommon. Thickening of the aortic and pulmonic valves sometimes is observed in older animals but rarely causes more than mild insufficiency.

#### **Etiology and Pathophysiology**

The cause of degenerative AV valve disease is unclear, but a hereditary basis is likely. Middle-aged and older small to mid-size breeds are most often affected. Disease prevalence and severity increase with age. About a third of small-breed dogs older than 10 years of age are affected. Commonly affected breeds include Toy and Miniature Poodles, Miniature Schnauzers, Chihuahuas, Pomeranians, Fox Terriers, Cocker Spaniels, Pekingese, Boston Terriers, Miniature Pinschers, Whippets, and Cavalier King Charles Spaniels. An especially high prevalence and an early onset of degenerative mitral valve disease (MVD) is reported in Cavalier King Charles Spaniels, in which inheritance is thought to be poly-

genic, with gender and age influencing expression. It appears that the overall prevalence of mitral regurgitation (MR) murmurs and degenerative valve disease is similar in male and female dogs, but males may have faster disease progression. Some large-breed dogs are affected also, and the prevalence may be higher in German Shepherd Dogs.

Multiple factors involving collagen degeneration, valve leaflet stress, and endothelial function are thought to be involved. Pathologic valve changes develop gradually with age. Early lesions consist of small nodules on the free margins of the valve; these become larger, coalescing plaques that thicken and distort the valve. The histologic changes have been described as *myxomatous degeneration*. Collagen within the affected leaflets degenerates, and acid mucopolysaccharides and other substances accumulate within the layers of the leaflets, resulting in nodular thickening, deformity, and weakening of the valve as well as its chordae tendineae. Redundant tissue between chordal attachments often bulges (prolapses) like a parachute or balloon toward the atrium. Mitral valve prolapse may be important in the pathogenesis of the disease, at least in some breeds.

Affected valves gradually begin to leak because their edges do not coapt properly. As the lesions progress, the valve insufficiency (regurgitation) becomes clinically evident. Atrial jet lesions; endocardial fibrosis; and, in patients with advanced disease, partial or even full-thickness atrial tears can form. Chronic valvular disease is also associated with intramural coronary arteriosclerosis, microscopic intramural myocardial infarctions, and focal myocardial fibrosis. The extent to which these changes cause clinical myocardial dysfunction is not clear; however, impaired myocardial contractility is observed late in the disease. Interestingly, senior dogs without valvular disease also have similar vascular lesions.

The pathophysiologic changes relate to volume overload on the affected side of the heart after the valve or valves become incompetent. Regurgitation usually develops slowly over months to years. Mean atrial pressure usually remains fairly low during this time, unless a sudden increase in regurgitant volume (e.g., ruptured chordae) occurs. With advancing valve degeneration, a progressively larger volume of blood moves ineffectually back and forth between the ven-

tricle and atrium, diminishing the forward flow to the aorta. Compensatory mechanisms augment blood volume to meet the circulatory needs of the body (see Chapter 3), including increased sympathetic activity, attenuated vagal tone, and renin-angiotensin-aldosterone system (RAAS) activation. Natriuretic peptide release occurs; higher atrial natriuretic peptide concentrations have been associated with marked left atrium (LA) enlargement and severe congestive heart failure (CHF). The affected ventricle and atrium dilate to accept the growing regurgitant volume and the required forward stroke volume; eccentric myocardial hypertrophy develops in an attempt to normalize the resulting increase in wall stress.

These compensatory changes in heart size and blood volume allow most dogs to remain asymptomatic for a prolonged period. Massive LA enlargement may develop before any signs of heart failure appear, and some dogs never show clinical signs of heart failure. The rate at which the regurgitation worsens, as well as the degree of atrial distensibility and ventricular contractility, influence how well the disease is tolerated. A gradual increase in atrial, pulmonary venous, and capillary hydrostatic pressures stimulates compensatory increases in pulmonary lymphatic flow. Overt pulmonary edema develops when the capacity of the pulmonary lymphatic system is exceeded. Tricuspid insufficiency may be severe enough to cause right-sided CHF. Increased pulmonary vascular pressure secondary to chronic left-sided CHF may also contribute to the development of right-sided heart failure.

Ventricular pump function is maintained fairly well until late in the disease in many dogs, even in the face of severe congestive signs. Nevertheless, chronic volume overload eventually reduces myocyte contractility. The mechanism of myocardial dysfunction may involve damage from oxygen free radicals as well as neurohormonal activation. Reduced contractility exacerbates ventricular dilation and valve regurgitation and therefore can worsen CHF. Assessment of left ventricular (LV) contractility in animals with MR is complicated by the fact that the most commonly used clinical indices (e.g., echocardiographic fractional shortening, ejection fraction) overestimate contractility because they are obtained during ejection and are therefore affected by the reduced ventricular afterload caused by MR. The echocardiographic estimation of the end-systolic volume index may be useful (see p. 41). This index suggests that myocardial function is normal to mildly depressed in most dogs with chronic mitral degeneration. A number of other echo/ Doppler indices can also help assess LV systolic and diastolic function.

# **Complicating Factors**

Although this disease usually progresses slowly, certain complicating events can precipitate acute clinical signs in dogs with previously compensated disease (Box 6-1). For example, tachyarrhythmias may be severe enough to cause decompensated CHF, syncope, or both. Frequent atrial premature contractions, paroxysmal atrial tachycardia, or atrial fibrilla-

tion can reduce ventricular filling time and cardiac output, increase myocardial oxygen needs, and worsen pulmonary congestion and edema. Ventricular tachyarrhythmias also occur but are less common.

Sudden rupture of diseased chordae tendineae acutely increases regurgitant volume and can precipitate fulminant pulmonary edema within hours in previously compensated or even asymptomatic dogs. Signs of low cardiac output may also occur. Sometimes, ruptured chordae tendineae are an incidental finding (on an echocardiogram or at necropsy), especially if second- or third-order chordae are involved.

Massive LA enlargement itself can result in compression of the left mainstem bronchus and stimulate persistent coughing, even in the absence of CHF. Furthermore, massive left (or right) atrial distention can result in partial- or fullthickness tearing. Atrial wall rupture usually causes acute cardiac tamponade; there appears to be a higher prevalence



BOX 6-1

Potential Complications of Chronic Atrioventricular Valve Disease

#### **Causes of Acutely Worsened Pulmonary Edema**

Arrhythmias

Frequent atrial premature complexes

Paroxysmal atrial/supraventricular tachycardia

Atrial fibrillation

Frequent ventricular tachyarrhythmias

Rule out drug toxicity (e.g., digoxin)

Ruptured chordae tendineae

latrogenic volume overload

Excessive volumes of IV fluids or blood

High-sodium fluids

Erratic or improper medication administration

Insufficient medication for stage of disease

Increased cardiac workload

Physical exertion

Anemia

Infections/sepsis

Hypertension

Disease of other organ systems (e.g., pulmonary, renal,

liver, endocrine)

Hot, humid environment

Excessively cold environment

Other environmental stresses

High salt intake

Myocardial degeneration and poor contractility

#### Causes of Reduced Cardiac Output or Weakness

Arrhythmias (see above)

Ruptured chordae tendineae

Cough-syncope

Left atrial tear

Intrapericardial bleeding

Cardiac tamponade

Increased cardiac workload (see above)

Secondary right-sided heart failure

Myocardial degeneration and poor contractility

of this complication in male Miniature Poodles, Cocker Spaniels, and Dachshunds. In most of these cases, severe valve disease; marked atrial enlargement; atrial jet lesions; and, often, ruptured first-order chordae tendineae are present.

#### **Clinical Features**

Degenerative AV valve disease may cause no clinical signs for years, and some dogs never develop signs of heart failure. In those that do, the signs usually relate to decreased exercise tolerance and manifestations of pulmonary congestion and edema. Diminished exercise capacity and cough or tachypnea with exertion are common initial owner complaints. As pulmonary congestion and interstitial edema worsen, the resting respiratory rate increases. Coughing tends to occur at night and early morning, as well as in association with activity. Severe edema results in obvious respiratory distress and usually a moist cough. Signs of severe pulmonary edema can develop gradually or acutely. Intermittent episodes of symptomatic pulmonary edema interspersed with periods of compensated heart failure occurring over months to years are also common. Episodes of transient weakness or acute collapse (syncope) can occur secondary to arrhythmias, coughing, or an atrial tear. Signs of tricuspid regurgitation (TR) are often overshadowed by those of MR but include ascites; respiratory distress from pleural effusion; and, rarely, subcutaneous edema. Splanchnic congestion may precipitate gastrointestinal signs. The cough caused by main bronchus compression often is described as "honking."

A holosystolic murmur heard best in the area of the left apex (left fourth to sixth intercostal space) is typical in patients with MR. The murmur can radiate in any direction. Mild regurgitation may be inaudible or cause a murmur only in early systole (protosystolic). Exercise and excitement often increase the intensity of soft MR murmurs. Louder murmurs have been associated with more advanced disease, but in dogs with massive regurgitation and severe heart failure, the murmur can be soft or even inaudible. Occasionally, the murmur sounds like a musical tone or whoop. Some dogs with chronic mitral disease have a mid- to late-systolic click, with or without a murmur. An S<sub>3</sub> gallop may be audible at the left apex in dogs with advanced disease. TR typically causes a holosystolic murmur best heard at the right apex. Features that aid in differentiating a TR murmur from radiation of an MR murmur to the right chest wall include jugular vein pulsations, a precordial thrill over the right apex, and a different quality to the murmur heard over the tricuspid region.

Pulmonary sounds can be normal or abnormal. Accentuated, harsh breath sounds and end-inspiratory crackles (especially in ventral lung fields) develop as pulmonary edema worsens. Fulminant pulmonary edema causes widespread inspiratory as well as expiratory crackles and wheezes. Some dogs with chronic MR have abnormal lung sounds caused by underlying pulmonary or airway disease rather than CHF. Dogs with CHF tend to have sinus tachycardia; those with chronic pulmonary disease frequently have

marked sinus arrhythmia and a normal heart rate. Pleural effusion causes diminished pulmonary sounds ventrally.

Other physical examination findings may be normal or noncontributory. Peripheral capillary perfusion and arterial pulse strength are usually good, although pulse deficits may be present in dogs with tachyarrhythmias. A palpable precordial thrill accompanies loud (grade 5-6/6) murmurs. Jugular vein distention and pulsations are not expected in dogs with MR alone. In animals with TR, jugular pulses occur during ventricular systole; these are more evident after exercise or in association with excitement. Jugular venous distention results from elevated right heart filling pressures. Jugular pulsations and distention are more evident with cranial abdominal compression (positive hepatojugular reflux). Ascites or hepatomegaly may be evident in dogs with right-sided CHF.

# Diagnosis

#### RADIOGRAPHY

Thoracic radiographs typically show some degree of LA and LV enlargement (see p. 13), which progresses over months to years (Fig. 6-1). As LA size increases, dorsal main bronchus displacement occurs. Severe LA enlargement causes compression of the left mainstem bronchus. Fluoroscopy may demonstrate dynamic main bronchus collapse during coughing or even quiet breathing in such animals. Extreme dilation of the LA can result over time, even without clinical heart failure. Variable right heart enlargement occurs with chronic TR, but this may be masked by left heart and pulmonary changes associated with concurrent MVD.

Pulmonary venous congestion and interstitial edema occur with the onset of left-sided CHF; progressive interstitial and alveolar pulmonary edema may follow. Although cardiogenic pulmonary edema in dogs typically has a hilar, dorsocaudal, and bilaterally symmetric pattern, an asymmetric distribution is seen in some dogs. The presence and severity of pulmonary edema do not necessarily correlate with the degree of cardiomegaly. Acute, severe MR (e.g., with rupture of the chordae tendineae) can cause severe edema in the presence of minimal LA enlargement. Conversely, slowly worsening MR can produce massive LA enlargement with no evidence of CHF. Early signs of right-sided heart failure include caudal vena caval distention, pleural fissure lines, and hepatomegaly. Overt pleural effusion and ascites occur with advanced failure.

#### ELECTROCARDOGRAPHY

The electrocardiogram (ECG) may suggest LA or biatrial enlargement and LV dilation (see p. 28), although the tracing is often normal. An RV enlargement pattern is occasionally seen in dogs with severe TR. Arrhythmias, especially sinus tachycardia, supraventricular premature complexes, paroxysmal or sustained supraventricular tachycardias, ventricular premature complexes, and atrial fibrillation are common in dogs with advanced disease. These arrhythmias may be associated with decompensated CHF, weakness, or syncope.

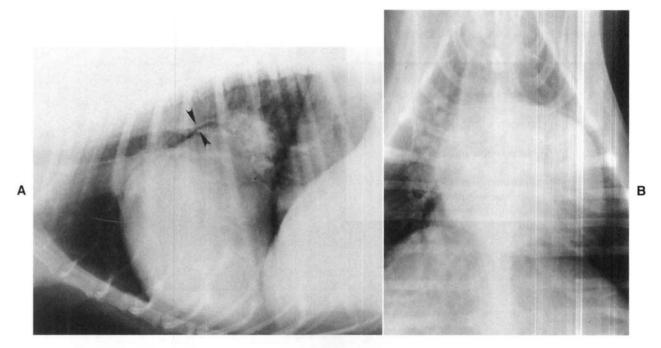


FIG 6-1
Lateral (A) and dorsoventral (B) radiographs from a Poodle with advanced mitral valve insufficiency. Note marked left ventricular and atrial enlargement and narrowing of left mainstem bronchus (arrowheads in A).

#### **ECHOCARDIOGRAPHY**

Echocardiography shows the atrial and ventricular chamber dilation secondary to chronic AV valve insufficiency. Depending on the degree of volume overload, this enlargement can be severe. Vigorous LV wall and septal motion are seen with MR when contractility is normal (Fig. 6-2); fractional shortening is high, and there is little to no E point-septal separation. Although ventricular diastolic dimension is increased, systolic dimension is normal until myocardial failure ensues. Calculation of end-systolic volume index may help in assessing myocardial function. Ventricular wall thickness is typically normal in dogs with chronic AV valve disease. With severe TR, paradoxical septal motion may occur along with the right ventricular (RV) and right atrial (RA) dilation. Pericardial fluid (blood) is seen after an LA tear, and evidence for cardiac tamponade may be evident. Mild pericardial effusion may also accompany signs of right-sided CHF.

Affected valve cusps are thickened and may appear knobby. Smooth thickening is characteristic of degenerative disease (endocardiosis). Conversely, rough and irregular vegetative valve lesions are characteristic of bacterial endocarditis; however, clear differentiation between these by echocardiography alone may be impossible. Systolic prolapse involving one or both valve leaflets is common with degenerative AV valve disease (Fig. 6-3, A). A ruptured chorda tendinea or leaflet tip sometimes is seen flailing into the atrium during systole (Figure 6-3, B). The direction and extent of flow disturbance can be seen with color-flow Doppler (see Figure 2-35). Although the size of the disturbed

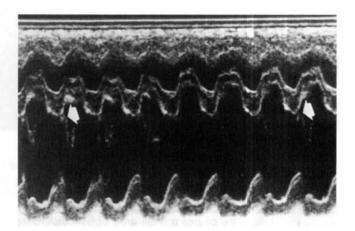
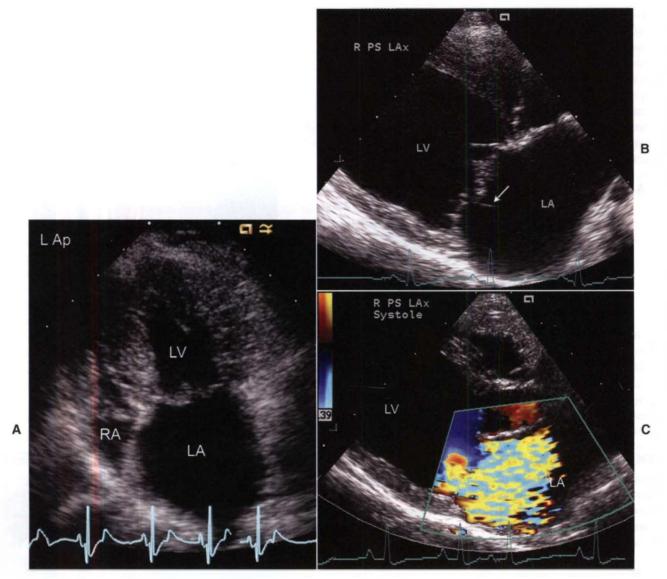


FIG 6-2
Sample M-mode echocardiogram from male Maltese with advanced mitral valve insufficiency and left-sided heart failure. Note accentuated septal and left ventricular posterior wall motion (fractional shortening = 50%) and lack of mitral valve E point-septal separation (arrows).

flow area provides a rough estimate of regurgitation severity, there are technical limitations with this. The proximal isovelocity surface area (PISA) method is considered by some to be a more accurate way to estimate MR severity. Other Doppler techniques can be used to evaluate systolic and diastolic ventricular function. Maximal TR jet velocity indicates whether pulmonary hypertension is present and its severity.



**FIG 6-3 A,** Thick, mildly prolapsing mitral valve and LA enlargement are seen from the left apical position in an older Dachshund with severe degenerative AV valve disease. The tricuspid valve is also thick. **B,** Chorda tendineae rupture is evident by the flail segment (arrow) seen in the enlarged LA of an older mixed breed dog. **C,** A large jet of mitral regurgitation causes a wide area of flow disturbance in another mixed breed dog on color flow echo. Note the LA and LV enlargement. LA, Left atrium; LV, left ventricle; RA, right atrium.

# **Clinicopathologic Findings**

Clinical laboratory data may be normal or reflect changes associated with CHF or concurrent extracardiac disease. Other diseases produce signs similar to those of CHF resulting from degenerative AV valve disease, including tracheal collapse, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary neoplasia, pneumonia, pharyngitis, heartworm disease, dilated cardiomyopathy, and bacterial endocarditis.

# **Treatment and Prognosis**

Medical therapy is used to control signs of CHF as well as support cardiac function and modulate the excessive neurohormonal activation that contributes to the disease process (Box 6-2). Drugs that decrease LV size (e.g., diuretics, vaso-dilators, positive inotropic agents) may reduce the regurgitant volume by decreasing mitral annulus size. Drugs that promote arteriolar vasodilation enhance forward cardiac output and reduce regurgitant volume by decreasing systemic arteriolar resistance. Frequent reevaluation and medication adjustment become necessary as the disease progresses. In many dogs with advanced MR, clinical compensation can be maintained for months to years using appropriate therapy. Although congestive signs develop gradually in some dogs, severe pulmonary edema or episodes of syncope appear acutely in others. Intermittent episodes of decompensation



#### Treatment Guidelines for Chronic Atrioventricular Valve Disease

# Asymptomatic (Modified AHA/ACC Stage B)

Client education (about disease process and early heart failure signs)

Routine health maintenance

Blood pressure measurement

Baseline chest radiographs (+/- echocardiogram) and yearly rechecks

Maintain normal body weight/condition

Regular mild to moderate exercise

Avoid excessively strenuous activity

Heartworm testing and prophylaxis in endemic areas

Manage other medical problems

Avoid high-salt foods; consider moderately salt-restricted

Consider ACE inhibitor if marked increase in LA +/- LV enlargement occurs; additional therapies aimed against neurohormonal activation may or may not be clinically useful

## Mild to Moderate CHF signs (Modified AHA/ACC Stage C, Chronic)\*

Considerations as above, and

Furosemide, as needed

ACE inhibitor (or pimobendan)

Pimobendan (can use with or without ACE inhibitor)

+/- Digoxin (indicated with atrial tachyarrhythmias, including fibrillation)

+/- Additional diuretic (spironolactone, hydrochlorothiazide) Antiarrhythmic therapy if necessary

Complete exercise restriction until signs abate

Moderate dietary salt restriction

Resting respiratory (+/- heart) rate monitoring at home

# Severe, Acute CHF Signs (Modified AHA/ACC Stage C, Acute)\*

Supplemental O<sub>2</sub>

Cage rest and minimal patient handling

Furosemide (more aggressive doses, parenteral)

Vasodilator therapy

Consider IV nitroprusside, or

Oral hydralazine or amlodipine, +/- topical nitroglycerine

+/- Butorphanol or morphine

Antiarrhythmic therapy, if necessary

+/- Positive inotropic drug:

If myocardial failure documented, IV drug can be used (see Box 3-1).

After patient stabilized, can use long-term oral pimobendan +/- digoxin therapy

+/- Bronchodilator

Thoracocentesis, if large volume pleural effusion

### **Chronic Recurrent or Refractory Heart Failure Strategies** (Modified AHA/ACC Stage D)\*

Ensure that therapies for stage C are being given at optimal doses and intervals, including furosemide, ACE inhibitor, pimobendan and/or digoxin, spironolactone

Rule out systemic arterial hypertension, arrhythmias, anemia, and other complications

Increase furosemide dose/frequency; may be able to decrease again in several days after signs abate

Enforced rest until signs abate

Add pimobendan, if not currently prescribed

Increase ACE inhibitor dose/frequency (to g12h from q24h)

Add digoxin, if not currently prescribed; monitor serum concentration; increase dose only if subtherapeutic concentration documented

Add (or increase dose of) second diuretic (e.g., spironolactone, hydrochlorothiazide)

Additional afterload reduction (e.g., amlodipine or hydralazine); monitor blood pressure

Further restrict dietary salt intake; verify that drinking water is low in sodium

Thoracocentesis (or abdomincentesis) as needed Manage arrhythmias, if present (see Chapter 4)

Consider sildenafil for secondary pulmonary hypertension

(e.g., 1-2 mg/kg q8-12h)

Consider bronchodilator trial, or cough suppressant

in dogs on long-term CHF therapy often can be successfully managed. Therapy must be guided by the patient's clinical status and the nature of complicating factors. Surgical procedures such as mitral annuloplasty, other valve repair techniques, and mitral valve replacement may be treatment options in some patients but are not widely available.

# **Asymptomatic Atrioventricular Valve Regurgitation**

Dogs that have shown no clinical signs of disease are generally not given drug therapy. Convincing evidence that angiotensin-converting enzyme inhibitor (ACEI) or other therapy delays time to CHF onset in asymptomatic dogs is presently lacking. Whether dogs with marked cardiomegaly might benefit from therapy to modulate pathologic remodeling is unclear.

Client education about the disease process and early signs of CHF is important. It is probably prudent to discourage high-salt foods, pursue weight reduction for obese dogs, and avoid prolonged strenuous exercise. A diet moderately reduced in salt may be helpful. Periodic reevaluation (e.g., every 6 to 12 months) of cardiac size and function as well as blood pressure is advised. Other disease conditions are managed as appropriate.

<sup>\*</sup> See Tables 3-2, 3-3, and Box 3-1 for further details and doses.

# Mild to Moderate Congestive Heart Failure

When clinical signs occur in association with exercise or activity, several treatment modalities are instituted (see Box 6-2 and Tables 3-3 and Box 3-1). The severity of clinical signs and the nature of any complicating factors influence the aggressiveness of therapy. When it is unclear whether respiratory signs are caused by early CHF or a noncardiac cause, a therapeutic trial of furosemide (e.g., 1 to 2 mg/kg by mouth q8-12h) is indicated. Cardiogenic pulmonary edema usually responds rapidly.

Furosemide is used for dogs with radiographic evidence of pulmonary edema and/or more severe clinical signs. Higher and more frequent doses are used when edema is severe. After signs of failure are controlled, the dose and frequency of furosemide administration are gradually reduced to the lowest effective levels for chronic therapy. Furosemide alone (e.g., without an ACEI or other agent) is not recommended for the long-term treatment of heart failure.

An ACEI is generally recommended for dogs with early signs of failure (see Chapter 3). The ability of these agents to modulate neurohormonal responses to heart failure is thought to be their main advantage. Chronic ACEI therapy can improve exercise tolerance, cough, and respiratory effort, although the issue of enhanced survival is unclear.

Pimobendan also is being used increasingly for the management of moderate to advanced CHF (see Chapter 3). This drug has positive inotropic, vasodilator, and other actions. Its beneficial effects may exceed those of ACEIs, although they are often used together. Digoxin, with or without pimobendan, is often added to the chronic therapy of CHF resulting from advanced AV valve insufficiency. Digoxin's sensitizing effect on baroreceptors may be more advantageous than its modest positive inotropic effect (see Chapter 3). Marked LV dilation, evidence for reduced myocardial contractility, or recurrent episodes of pulmonary edema despite furosemide and other treatment are indications for adding digoxin. Digoxin also is indicated for heart rate control in dogs with atrial fibrillation and for its antiarrhythmic effect in some cases of frequent atrial premature beats or supraventricular tachycardia. Conservative doses and measurement of serum concentrations are recommended to prevent toxicity (see p. 66).

Moderate dietary salt restriction (e.g., diets formulated for dogs with kidney disease or for senior dogs) is recommended initially. Further salt restriction may be achieved with diets formulated for patients with heart failure. Exercise restriction is important when signs of CHF exist. Mild to moderate, regular activity (not causing undue respiratory effort) may be resumed during chronic, compensated disease. Strenuous exercise is not recommended. Antitussive therapy can be helpful in dogs without pulmonary edema but with persistent cough caused by mechanical mainstem bronchus compression (e.g., hydrocodone bitartrate, 0.25 mg/kg by mouth q8-12h; or butorphanol, 0.5 mg/kg by mouth q6-12h).

# Severe Congestive Heart Failure

Severe pulmonary edema and shortness of breath at rest require urgent treatment (see Box 3-1). Aggressive diuresis with parenteral furosemide (e.g., 2 to 4 mg/kg q1-4h IV, initially), supplemental oxygen, and cage rest are instituted as soon as possible. Gentle handling is important because added stress may precipitate cardiopulmonary arrest. Thoracic radiographs and other diagnostic procedures are postponed until the animal's respiratory condition is more stable.

Vasodilator therapy is also indicated. If adequate monitoring facilities are available, intravenous (IV) nitroprusside may be used for rapid arteriolar and venous dilation; however, blood pressure must be closely monitored to prevent hypotension. Another approach for acute therapy is oral hydralazine. Its direct and rapid arteriolar vasodilating effect increases forward flow and decreases regurgitation; however, oral administration can be stressful. A reduced dose is used in animals already on an ACEI. Amlodipine is an alternative arteriolar vasodilator, but it has a much slower onset of action. Topical nitroglycerin also can be used in an attempt to reduce pulmonary venous pressure by direct venodilation.

When positive inotropic therapy is indicated, pimobendan (or digoxin) may be initiated (or continued if previously prescribed) once acute dyspnea subsides. Paroxysmal atrial tachycardia or atrial fibrillation may respond to digoxin. Although several days are needed to achieve a therapeutic blood concentration with oral maintenance doses, IV digitalization is generally not recommended. Diltiazem or a  $\beta$ -blocker (see Table 4-2) can be used instead of or in addition to digoxin if supraventricular tachyarrhythmias require treatment (see Chapter 4). Dogs that need more intense inotropic support or that have persistent hypotension can be given an IV agent (e.g., dobutamine, dopamine, amrinone; see Box 3-1).

Ancillary therapy often includes mild sedation to reduce anxiety (e.g., butorphanol or morphine). A bronchodilator (e.g., theophylline, aminophylline) may be useful if bronchospasm is induced by severe pulmonary edema; although efficacy for this is unclear, these agents may help support respiratory muscle function.

Thoracocentesis is indicated in dogs with moderate- to large-volume pleural effusion to improve pulmonary function. Ascites that impedes respiration also should be drained. Therapy for ventricular tachyarrhythmias is warranted in some cases. Close monitoring is important for titrating therapy and identifying drug toxicities or adverse effects (e.g., azotemia, electrolyte abnormalities, hypotension, arrhythmias).

After the animal's condition is stabilized, medications are adjusted over several days to weeks to determine optimal long-term therapy. Furosemide is titrated to the lowest dose (and longest interval) that controls signs of CHF. Institution of an ACEI is recommended for ongoing therapy if hydralazine or nitroprusside was the initial vasodilator used. As the effects of previously administered hydralazine wane, the first dose of ACEI given should be half the usual dose

(i.e., 0.25 mg/kg by mouth). An ACEI can be started at the standard dose shortly after discontinuing a nitroprusside infusion.

# **Chronic Management of Advanced Disease**

When CHF becomes refractory, therapy is intensified or modified according to individual patient needs. The following suggestions for modifying therapy are listed in approximate order of use. Recurrent pulmonary edema in some dogs responds to an increased dose of furosemide and rest for a few days. The dose can then be returned to previous or a slightly higher level, if possible. The ACEI dose should be maximized if this has not already been done (e.g., enalapril from once to twice daily).

Pimobendan and/or digoxin can be added if it is not already being used. The dose of digoxin is not titrated upward unless subtherapeutic serum concentrations are documented (see Chapter 3). Spironolactone can be added, if not already being used (see Chapter 3). This aldosterone antagonist may reduce the severity of chronic refractory pulmonary edema or effusions as well as have beneficial effects on cardiac remodeling. Conversely, another diuretic with a different mechanism of action or the spironolactone/hydrochlorothiazide combination product may be useful.

Continued monitoring, especially of renal function and serum electrolyte concentrations, is important. Dietary sodium restriction can be intensified. If the ACEI and furosemide doses are already maximal, low-dose hydralazine (e. g., 0.25 to 0.5 mg/kg by mouth q12h) or amlodipine (e.g., 0.05 to 0.2 mg/kg by mouth q24h) can be added, although blood pressure should be monitored.

Intermittent tachyarrhythmias can promote decompensated CHF as well as episodes of transient weakness or syncope. Cough-induced syncope, atrial rupture, or other causes of reduced cardiac output may also occur. Despite the periodic recurrence of signs of CHF, many dogs with chronic AV valve regurgitation can enjoy a good quality of life for several years after the signs of failure first appear.

# **Patient Monitoring and Reevaluation**

Client education regarding the disease process, the clinical signs of failure, and the drugs used to control them is essential for long-term therapy to be successful. As the disease progresses, medication readjustment (i.e., different dosages of currently used drugs and/or additional drugs) is expected. Several common potential complications of chronic degenerative AV valve disease can cause decompensation (see Box 6-1). At-home monitoring is important to detect early signs of decompensation. Respiratory (+/- heart) rate can be monitored periodically when the dog is quietly resting or sleeping (see p. 70; a persistent increase in either can signal early decompensation.

Asymptomatic dogs should be reevaluated at least yearly in the context of a routine preventive health program. The frequency of reevaluation in dogs receiving medication for heart failure depends on the disease severity and whether any complicating factors are present. Dogs with recently diag-

nosed or decompensated CHF should be evaluated more frequently (within several days to a week or so) until their condition is stable. Those with chronic heart failure that appears well-controlled can be reevaluated less frequently, usually several times per year. The medication supply, administration compliance, drugs and doses being given, and diet should be reviewed with the owner at each visit.

A general physical exam with particular attention to cardiovascular parameters is important at each visit. An ECG is indicated if an arrhythmia or unexpectedly low or high heart rate is found. When an arrhythmia is suspected but not documented on routine ECG, ambulatory electrocardiography (e.g., 24-hour Holter monitoring) can be helpful. The respiratory rate and pattern are also noted; thoracic radiographs are warranted if abnormal pulmonary sounds are heard or if the owner reports coughing, other respiratory signs, or an increased resting respiratory rate. Other causes of cough should be considered if neither pulmonary edema nor venous congestion is seen radiographically and if the resting respiratory rate has not increased. Left mainstem bronchus compression by an enlarged LA can stimulate a dry cough. Cough suppressants are helpful for this, but they should be prescribed only after other causes of cough are ruled out.

Echocardiography may show evidence of chordal rupture, progressive cardiomegaly, or worsened myocardial function. Frequent monitoring of serum electrolyte concentrations and renal function is important. Other routine blood and urine tests are done periodically also. Dogs receiving digoxin should have a serum concentration measured 7 to 10 days after treatment initiation or a dosage change. Additional measurements are recommended if signs consistent with toxicity appear or if renal disease or electrolyte imbalance (hypokalemia) is suspected.

The prognosis in dogs that have shown clinical signs of degenerative valve disease is quite variable. With appropriate therapy and attentive management of complications, some dogs live well for more than 4 years after the signs of heart failure first appear. Some dogs die during an initial episode of fulminant pulmonary edema. Survival for most symptomatic dogs ranges from several months to a few years.

# INFECTIVE ENDOCARDITIS

# **Etiology and Pathophysiology**

Endocarditis is more common in dogs than in cats. Bacteremia, either persistent or transient, is necessary for endocardial infection to occur. Recurrent bacteremia may occur with infections of the skin, mouth, urinary tract, prostate, lungs, or other organs. Dentistry procedures are known to cause a transient bacteremia. Other procedures are presumed to cause transient bacteremia in some cases (e.g., endoscopy, urethral catheterization, anal surgery, and other "dirty" procedures). The likelihood of a cardiac infection becoming established is increased when organisms are highly virulent or the bacterial load is heavy.

The endocardial surface of the valve is infected directly from the blood flowing past it. Previously normal valves may be invaded by virulent bacteria, causing acute bacterial endocarditis. Subacute bacterial endocarditis is thought to result from infection of previously damaged or diseased valves after a persistent bacteremia. Such damage may result from mechanical trauma (e.g., jet lesions resulting from turbulent blood flow or endocardial injury from a vascular catheter extending into the heart). Myxomatous degeneration of the mitral valve has not been associated with a higher risk for infective endocarditis.

The lesions of endocarditis are typically located downstream from the disturbed blood flow; common sites include the ventricular side of the aortic valve in patients with subaortic stenosis, the right ventricular side of a ventricular septal defect, and the atrial surface of a regurgitant mitral valve. Bacterial clumping caused by the action of an agglutinating antibody may facilitate attachment to the valves. Alternatively, chronic stress and mechanical trauma can predispose to the development of nonbacterial thrombotic endocarditis, a sterile accumulation of platelets and fibrin on the valve surface. Nonseptic emboli may break off from such vegetations and cause infarctions elsewhere. Bacteremia can also cause a secondary infective endocarditis at these sites.

The most common organisms identified in dogs and cats with endocarditis have been *Streptococcus* sp., *Staphylococcus* sp., and *Escherichia coli*. Additional organisms isolated from infected valves have included *Corynebacterium* (*Arcanobacterium*) sp., *Pasteurella* sp., *Pseudomonas aeruginosa*, *Erysipelothrix rhusiopathiae* (*E. tonsillaris*), and others. *Bartonella vinsonii* subsp. *berkhoffii* and other *Bartonella* sp. have also been found in dogs with endocarditis. Culture-negative endocarditis may be caused by fastidious organisms or by *Bartonella* spp.; in a recent study of 71 dogs with infective endocarditis, *Bartonella* spp. was identified as the causative agent in 45% of the patients with a negative blood culture and in 20% of the overall population.

The mitral and aortic valves are most commonly affected in dogs and cats. Microbial colonization leads to ulceration of the valve endothelium. Subendothelial collagen exposure in turn stimulates platelet aggregation and activation of the coagulation cascade, leading to the formation of vegetations. Vegetations consist mainly of aggregated platelets, fibrin, blood cells, and bacteria. Newer vegetations are friable. With time, the lesions become fibrous and may calcify. As additional fibrin is deposited over bacterial colonies, they become protected from normal host defenses as well as many antibiotics. Although vegetations usually involve the valve leaflets, lesions may extend to the chordae tendineae, sinuses of Valsalva, mural endocardium, or adjacent myocardium. Vegetations cause valve deformity, including perforations or tearing of the leaflet(s), and result in valve insufficiency. Rarely, large vegetations may cause the valve to become stenotic.

Valve insufficiency and subsequent volume overload commonly lead to CHF. Because the mitral and/or aortic valve is usually affected, left-sided CHF signs of pulmonary congestion and edema are usual. Clinical heart failure develops rapidly in patients with severe valve destruction, rupture of chordae tendineae, and multiple valve involvement, or when other predisposing factors are present. Cardiac function can be compromised by myocardial injury resulting from coronary arterial embolization with myocardial infarction and abscess formation or from direct extension of the infection into the myocardium. Reduced contractility and atrial or ventricular tachyarrhythmias often result. Aortic valve endocarditis lesions may extend into the AV node and cause partial or complete AV block. Arrhythmias may cause weakness, syncope, and sudden death or contribute to the development of CHF.

Fragments of vegetative lesions often break loose. Embolization of other body sites causes infarction or metastatic infection, which results in diverse clinical signs. Larger and more mobile vegetations (based on echocardiographic appearance) are associated with higher incidence of embolic events in people; the same may occur in animals. Emboli can be septic or bland (containing no infectious organisms). Septic arthritis, diskospondylitis, urinary tract infections, and renal and splenic infarctions are common in affected animals. Local abscess formation resulting from septic thromboemboli contributes to recurrent bacteremia and fever. Hypertrophic osteopathy has also been associated with bacterial endocarditis. Circulating immune complexes as well as cell-mediated responses contribute to the disease syndrome. Sterile polyarthritis, glomerulonephritis, vasculitis, and other forms of immune-mediated organ damage are common. Rheumatoid factor and antinuclear antibody test (ANA) results may be positive.

#### **Clinical Features**

The prevalence of bacterial endocarditis is relatively low in dogs and even lower in cats. Male dogs are affected more commonly than females. An increased prevalence of endocarditis has been noted in association with age. German Shepherd Dogs and other large-breed dogs may be at greater risk. Subaortic stenosis is a known risk factor for aortic valve endocarditis. Immunocompromised animals may also be at greater risk for endocarditis, but this has not been substantiated.

The clinical signs of endocarditis are quite variable. Many affected animals have evidence of past or concurrent infections, although often a clear history of predisposing factors is absent. The presenting signs can result from left-sided CHF or arrhythmias, but cardiac signs may be overshadowed by signs of systemic infarction, infection, immune-mediated damage, or a combination of these. Nonspecific signs of lethargy, weight loss, inappetence, recurrent fever, and weakness may be the predominant abnormalities. Infective endocarditis often mimics immune-mediated disease. Dogs with endocarditis are commonly evaluated for a "fever of unknown origin." Some of the consequences of infectious endocarditis are outlined in Box 6-3. Endocarditis has been nicknamed "the great imitator"; maintaining an index of suspicion for this disease is important.



BOX 6-3

# Potential Sequelae of Infective Endocarditis

#### Heart

Valve insufficiency or stenosis

Murmur

Congestive heart failure

Coronary embolization (aortic valve\*)

Myocardial infarction Myocardial abscess Myocarditis

Decreased contractility (segmental or global)

Arrhythmias

Myocarditis (direct invasion by microorganisms)

**Arrhythmias** 

Atrioventricular conduction abnormalities (aortic valve\*)

Decreased contractility

Pericarditis (direct invasion by microorganisms)

Pericardial effusion Cardiac tamponade (?)

#### Kidney

Infarction

Reduced renal function

Abscess formation and pyelonephritis

Reduced renal function Urinary tract infection

Renal pain

Glomerulonephritis (immune mediated)

Proteinuria

Reduced renal function

#### Musculoskeletal

Septic arthritis

Joint swelling and pain

Lameness

Immune-mediated polyarthritis

Shifting-leg lameness

Joint swelling and pain

Septic osteomyelitis

Bone pain

Lameness

Myositis

Muscle pain

#### **Brain and Meninges**

Abscesses

Associated neurologic signs Encephalitis and meningitis

Associated neurologic signs

#### Vascular System in General

Vasculitis

Thrombosis

Petechiae and small hemorrhages (e.g., eye, skin)

Obstruction

Ischemia of tissues served, with associated signs

Pulmonary emboli (tricuspid or pulmonic valves, rare\*) Pneumonia (tricuspid or pulmonic valves, rare\*)

#### Nonspecific

Sepsis

Fever

Anorexia

Malaise and depression

Shaking

Vague pain

Inflammatory leukogram

Mild anemia

± Positive antinuclear antibody test

± Positive blood cultures

Infective valve damage may be signaled by signs of CHF in an unexpected clinical setting or in an animal with a murmur of recent onset, especially if other suggestive signs are present. But a "new" murmur can indicate noninfective acquired disease (e.g., degenerative valve disease, cardiomyopathy), previously undiagnosed congenital disease, or physiologic alterations (e.g., fever, anemia). Conversely, endocarditis may develop in an animal known to have a murmur resulting from another cardiac disease. Although a change in murmur quality or intensity over a short time frame may indicate active valve damage, physiologic causes of murmur variation are common. The onset of a diastolic murmur at the left heartbase is suspicious for aortic valve endocarditis, especially if fever or other signs are present.

# Diagnosis

It may be difficult to obtain a definitive antemortem diagnosis. Presumptive diagnosis of infective endocarditis is made on the basis of positive findings in two or more blood cultures, in addition to either echocardiographic evidence of vegetations or valve destruction or the documented recent appearance of a regurgitant murmur. Endocarditis is likely even when blood culture results are negative or intermittently positive if there is echocardiographic evidence of vegetations or valve destruction along with a combination of other criteria (Box 6-4). A new diastolic murmur, hyperkinetic pulses, and fever are strongly suggestive of aortic valve endocarditis.

Several samples of at least 10 ml of blood should be aseptically collected over a 24-hour period for bacterial blood

<sup>\*</sup> Diseased valve most commonly associated with abnormality.



Criteria for Diagnosis of Infectious Endocarditis\*

#### **Definite Endocarditis by Pathologic Criteria**

Pathologic (postmortem) lesions of active endocarditis with evidence of microorganisms in vegetation (or embolus) or intracardiac abcess

#### **Definite Endocarditis by Clinical Criteria**

Two major criteria (below), or One major and three minor criteria, or Five minor criteria

#### **Possible Endocarditis**

Findings consistent with infectious endocarditis that fall short of "definite" but not "rejected"

#### Rejected Diagnosis of Endocarditis

Firm alternative diagnosis for clinical manifestations
Resolution of manifestations of infective endocarditis with 4
or fewer days of antibiotic therapy

No pathologic evidence of infective endocarditis at surgery or necropsy after 4 or fewer days of antibiotic therapy

#### **Major Criteria**

Positive blood cultures

Typical microorganism for infective endocarditis from two separate blood cultures Persistently positive blood cultures for organism consistent with endocarditis (samples drawn >12 h apart or three or more cultures drawn at least 1 h apart)

Evidence of endocardial involvement

Positive echocardiogram for infective endocarditis (oscillating mass on heart valve or supportive structure or in path of regurgitant jet or evidence of cardiac abcess). New valvular regurgitation (increase or change in preexisting murmur not sufficient evidence).

#### **Minor Criteria**

Predisposing heart condition (see p. 126)

Vascular phenomena: major arterial emboli, septic infarcts Immunologic phenomena: glomerulonephritis, positive antinuclear antibody or rheumatoid factor tests

Microbiologic evidence: positive blood culture not meeting major criteria above

Echocardiogram consistent with infective endocarditis but not meeting major criteria above

(Rare in dogs and cats: repeated nonsterile IV drug administration)

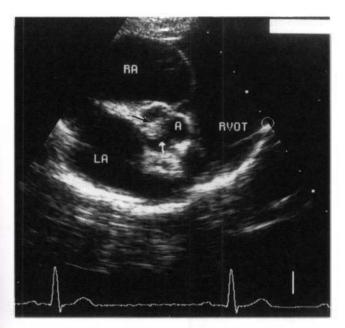
\* Adapted from Duke criteria for endocarditis. In Durack DT et al: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings, Am J Med 96:200, 1994.

culture, with more than 1 hour elapsing between collections. Ideally, different venipuncture sites should be used for each sample. Larger sample volumes (e.g., 20 to 30 ml) increase culture sensitivity. Both aerobic and anaerobic cultures have been recommended, although the value of routine anaerobic culture is questionable. Prolonged incubation (3 weeks) is recommended because some bacteria are slow-growing. Although blood culture results are positive in many dogs with this disease, negative results do not necessarily rule out infective endocarditis; in a recent study, less than 50% of the blood cultures in dogs with confirmed infective endocarditis were positive. As discussed above, Bartonella spp. is an emerging pathogen that causes blood culture-negative endocarditis in dogs; in the same study, 45% of the dogs with negative blood cultures were positive for Bartonella spp. on polymerase chain reaction (PCR). Results may be negative in the setting of chronic endocarditis, recent antibiotic therapy, intermittent bacteremia, and infection with fastidious or slow-growing organisms, as well as noninfective endocarditis. Serologic and PCR testing are also commercially available for Bartonella spp.

Echocardiography is especially supportive if oscillating vegetative lesions and abnormal valve motion can be identified (Fig. 6-4). The visualization of lesions depends on their size and location, on the image resolution, and

the proficiency of the echocardiographer. Because falsenegative and false-positive findings of "lesions" may occur, cautious interpretation of images is important. Mild valve thickening and/or enhanced echogenicity may occur in patients with early valve damage. Vegetative lesions appear as irregular dense masses. As valve destruction progresses, ruptured chordae, flail leaflet tips, or other abnormal valve motion can be seen. Differentiation of mitral vegetations from degenerative thickening may be impossible, however, especially in the early stages. Nevertheless, vegetative endocarditis classically causes rough, ragged-looking valve thickening; degenerative disease is associated with smooth valvular thickening. Poor or marginal-quality images or the use of lower-frequency transducers can prevent identification of some vegetations because of suboptimal resolution. Secondary effects of valve dysfunction include chamber enlargement from volume overload and flail or otherwise abnormal valve leaflet motion. Myocardial dysfunction and arrhythmias may also be evident. Aortic insufficiency can cause fluttering of the anterior mitral valve leaflet during diastole as the regurgitant jet makes contact with this leaflet. Doppler studies illustrate flow disturbances (Fig. 6-5).

The ECG may be normal or document premature beats, tachycardias, conduction disturbances, or evidence of myo-



#### FIG 6-4

Right parasternal short-axis echocardiogram at the aortic-left atrial level in a 2-year-old male Vizsla with congenital subaortic stenosis and pulmonic stenosis. Note the aortic valve vegetation (arrows) caused by endocarditis. A, Aorta; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract.

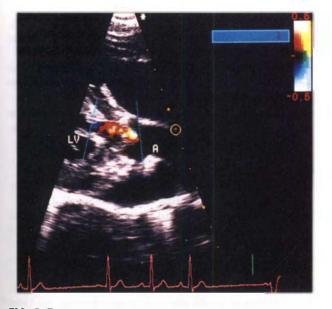


FIG 0-5

Right parasternal long axis, color flow Doppler image taken during diastole from the same dog as in Fig 6-4. The "flamelike" jet of aortic regurgitation extends from the closed aortic valve into the left ventricular outflow tract. A, Aorta; LV, left ventricle.

cardial ischemia. Radiographic findings are unremarkable in some cases; however, in others, evidence of left-sided CHF or other organ involvement (e.g., diskospondylitis) is seen. Cardiomegaly is minimal early in the disease but progresses over time as a result of valve insufficiency.

Clinicopathologic findings usually reflect an inflammatory process. Neutrophilia with a left shift is typical of acute endocarditis, whereas mature neutrophilia with or without monocytosis usually develops with chronic disease. Nonregenerative anemia has been associated with about half of canine cases. Biochemical abnormalities are variable. Azotemia, hyperglobulinemia, hematuria, pyuria, and proteinuria are common. The ANA results may be positive in dogs with subacute or chronic bacterial endocarditis; in a recent study, 75% of dogs with *Bartonella vinsonii* infection had positive ANA test results.

# **Treatment and Prognosis**

Aggressive therapy with bactericidal antibiotics capable of penetrating fibrin, as well as supportive care, are indicated for infective endocarditis. Ideally, drug choice is guided by culture and in-vitro susceptibility test results. Because treatment delay while waiting for these results can be harmful, broad-spectrum combination therapy is usually begun immediately after blood culture samples are obtained. Therapy can be altered, if necessary, when culture results are available. Culture-negative cases should be continued on the broad-spectrum regimen. An initial combination of a cephalosporin, penicillin, or a synthetic penicillin derivative (e.g., ampicillin) with an aminoglycoside (gentamicin or amikacin) or a fluoroquinolone (e.g. enrofloxacin) is commonly used. This is likely to be effective against the organisms most often associated with infective endocarditis. Clindamycin or metronidazole provides added anaerobic efficacy. Azithromycin or possibly enrofloxacin or high-dose doxycycline has been suggested for Bartonella spp.

Antibiotics are administered intravenously (or at least intramuscularly) for the first week or longer to obtain higher and more predictable blood concentrations. Oral therapy is often used thereafter for practical reasons, although parenteral administration is probably better. Antimicrobial therapy is continued for at least 6 weeks; 8 weeks of therapy is often recommended. However, aminoglycosides are discontinued after 1 week or sooner if renal toxicity develops. Close monitoring of the urine sediment is indicated to detect early aminoglycoside nephrotoxicity. For documented or suspected *B. vinsonii* (berkhoffii) infection, repeat serologic or PCR testing is recommended between 3 and 6 months after antibiotic therapy.

Supportive care includes management for CHF (see Chapter 3) and arrhythmias (see Chapter 4) if present. Complications related to the primary source of infection, embolic events, or immune responses are addressed to the extent possible. Attention to hydration status, nutritional support, and general nursing care is also important. Corticosteroids are contraindicated. The efficacy of aspirin to inhibit platelet aggregation and vegetative lesion growth and reduce the risk of embolic events is unknown. Aspirin or oral anticoagulants appear to be of no benefit for this in people.

Long-term prognosis is generally guarded to poor. Echocardiographic evidence of vegetations and volume overload suggests a poor prognosis. Aggressive therapy may be successful if valve dysfunction is not severe and large vegetations are absent. CHF is the most common cause of death, although sepsis, systemic embolization, arrhythmias, or renal failure may be the proximate cause.

The use of prophylactic antibiotics is controversial. Experience in people indicates that most cases of infective endocarditis are not preventable. The risk of endocarditis from a specific (e.g., dental) procedure in humans is very low compared with the cumulative risk associated with normal daily activities. However, because endocarditis appears to have an increased incidence in patients with certain cardiovascular malformations, antimicrobial prophylaxis is recommended before dental or other "dirty" procedures (e.g., involving the oral cavity or intestinal or urogenital systems) in these cases. Subaortic stenosis is a well-recognized predisposing lesion; endocarditis has also been associated with ventricular septal defect, patent ductus arteriosus, and cyanotic congenital heart disease. Antimicrobial prophylaxis is recommended for animals with an implanted pacemaker or other device or with a history of endocarditis. Prophylaxis should be considered for immunocompromised animals as well. Recommendations (extrapolated from human medicine) include the administration of high-dose ampicillin or amoxicillin 1 hour before and 6 hours after an oral or upper respiratory procedure and ampicillin with an aminoglycoside (IV, 30 minutes before and 8 hours after) a gastrointestinal or urogenital procedure. Alternatively, ticarcillin or a first-generation cephalosporin intravenously 1 hour before and 6 hours after the procedure has been used.

# Suggested Readings

#### DEGENERATIVE AV VALVE DISEASE

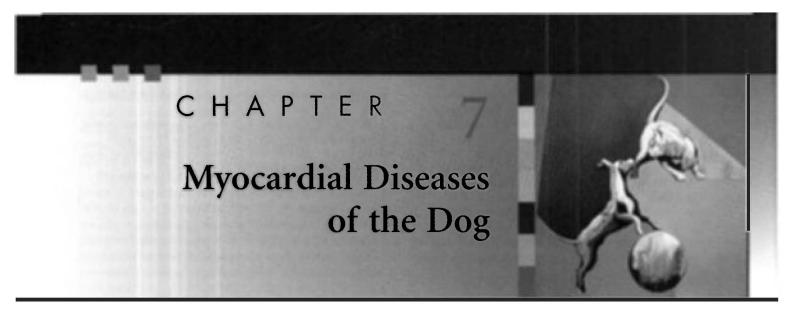
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# CHAPTER OUTLINE

#### DILATED CARDIOMYOPATHY

Radiography

Electrocardiography

Echocardiography

Clinicopathologic Findings

Occult Dilated Cardiomyopathy

Clinically Evident Dilated Cardiomyopathy

# ARRHYTHMOGENIC RIGHT VENTRICULÁR

CARDIOMYOPATHY

Cardiomyopathy in Boxers

Arrhythmogenic Right Ventricular Cardiomyopathy

in NonBoxer Dogs

#### SECONDARY MYOCARDIAL DISEASE

Myocardial Toxins

Metabolic and Nutritional Deficiency

Ischemic Myocardial Disease

Tachycardia-Induced Cardiomyopathy

# HYPERTROPHIC CARDIOMYOPATHY

Clinical Features

Diagnosis

Treatment

#### **MYOCARDITIS**

Infective Myocarditis

Non-Infective Myocarditis

Traumatic Myocarditis

Heart muscle disease that leads to contractile dysfunction and cardiac chamber enlargement is an important cause of heart failure in dogs. Idiopathic or primary dilated cardiomyopathy (DCM) is most common and mainly affects the larger breeds. Secondary and infective myocardial diseases (see pp. 135 and 137) occur less often. Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as Boxer cardiomyopathy, is an important myocardial disease in Boxers. ARVC is uncommon in other breeds. Hypertrophic cardiomyopathy (HCM) is recognized infrequently in dogs (see p. 137).

# DILATED CARDIOMYOPATHY

# **Etiology and Pathophysiology**

DCM is an idiopathic disease characterized by poor myocardial contractility, with or without arrhythmias. A genetic basis is thought to exist for idiopathic DCM, especially in breeds that have a high prevalence or a familial occurrence of the disease. Large and giant breeds are most commonly affected, including Doberman Pinschers, Great Danes, Saint Bernards, Scottish Deerhounds, Irish Wolfhounds, Boxers, Newfoundlands, Afghan Hounds, and Dalmatians. Some smaller breeds such as Cocker Spaniels and Bulldogs are also affected. The disease in rarely seen in dogs that weigh less than 12 kg. In at least some Great Danes, DCM appears to be an X-linked recessive trait. An autosomal dominant inheritance pattern was found in Boxers with ventricular arrhythmias (discussed in more detail later in this chapter); however, a rapidly fatal familial DCM affecting very young Portuguese Water Dogs shows an autosomal recessive inheritance pattern. Doberman Pinschers appear to have the highest prevalence of DCM; although a genetic basis is suspected, the inheritance pattern is not clear.

Various biochemical defects, nutritional deficiencies, toxins, immunologic mechanisms, and infectious agents may be involved in the pathogenesis of DCM in different cases. Impaired intracellular energy homeostasis and decreased myocardial adenosine triphosphate (ATP) concentrations were found in myocardial biochemical studies of affected Doberman Pinschers. DCM as an entity probably represents the end-stage of different pathologic processes or metabolic defects involving myocardial cells or the intercellular matrix rather than a single disease. Idiopathic DCM has also been associated with prior viral infections in people. However, on the basis of polymerase chain reaction (PCR) analysis of myocardial samples from a small number of DCM-affected dogs, viral agents do not seem to be commonly associated with DCM in this species.

Decreased ventricular contractility (systolic dysfunction) is the major functional defect in dogs with DCM. Progressive cardiac chamber dilation (remodeling) develops as systolic pump function and cardiac output worsen and compensa-

tory mechanisms become activated. Poor cardiac output can cause weakness, syncope, and ultimately, cardiogenic shock. Increased diastolic stiffness also contributes to the development of higher end-diastolic pressures, venous congestion, and congestive heart failure (CHF). Cardiac enlargement and papillary muscle dysfunction often cause poor systolic apposition of mitral and tricuspid leaflets with valve insufficiency. Although severe degenerative atrioventricular (AV) valve disease is not typical in dogs with DCM, some have mild to moderate valvular disease, which exacerbates valve insufficiency.

As cardiac output decreases, sympathetic, hormonal, and renal compensatory mechanisms become activated. These mechanisms increase heart rate, peripheral vascular resistance, and volume retention (see Chapter 3). Chronic neurohormonal activation is thought to contribute to progressive myocardial damage, as well as to CHF. Coronary perfusion can be compromised by poor forward blood flow and increased ventricular diastolic pressure; myocardial ischemia further impairs myocardial function and predisposes to arrhythmia development. Signs of low-output heart failure and right- or left-sided CHF (see Chapter 3) are common in dogs with DCM.

Atrial fibrillation (AF) often develops in dogs with DCM. Atrial contraction contributes importantly to ventricular filling, especially at faster heart rates. The loss of the "atrial kick" associated with AF reduces cardiac output and can cause acute clinical decompensation. Persistent tachycardia associated with AF probably also accelerates disease progression. Ventricular tachyarrhythmias also occur frequently and can cause sudden death. In Doberman Pinschers serial Holter recordings have documented the appearance of ventricular premature contractions (VPCs) months to more than a year before early echocardiographic abnormalities were noted. Once left ventricular (LV) function begins to deteriorate, the frequency of tachyarrhythmias increases. Excitement-induced bradyarrhythmias have also been associated with low-output signs in Doberman Pinschers.

Dilation of all cardiac chambers is typical in dogs with DCM, although left atrial (LA) and LV enlargement usually predominate. The ventricular wall thickness may appear decreased compared with the lumen size. Flattened, atrophic papillary muscles and endocardial thickening are described. Concurrent degenerative changes of the AV valves are generally only mild to moderate, if present at all. Histopathologic findings include scattered areas of myocardial necrosis, degeneration, and fibrosis, especially in the left ventricle. Narrowed (attenuated) myocardial cells with a wavy appearance may be a common finding. Inflammatory cell infiltrates, myocardial hypertrophy, and fatty infiltration (mainly in Boxers and some Doberman Pinschers) are inconsistent features.

# **Clinical Findings**

The prevalence of DCM increases with age, although most dogs presented with CHF are 4 to 10 years old. Males appear to be affected more often than females. However, in Boxers

and Doberman Pinschers there may be no gender predilection once dogs with occult disease are included. Cardiomyopathy in Boxers is described in more detail later (see p. 134). Male Doberman Pinschers generally show signs at an earlier age than females.

DCM appears to develop slowly, with a prolonged preclinical (occult) stage that may evolve over several years before clinical signs become evident. Occult DCM often is recognized through the use of echocardiography. Some giant-breed dogs with mild-to-moderate LV dysfunction are relatively asymptomatic, even in the presence of AF.

Clinical signs of DCM may appear to develop rapidly, especially in sedentary dogs in which early signs may not be noticed. Sudden death before CHF signs develop is relatively common. Presenting complaints include any or all of the following: weakness, lethargy, tachypnea or dyspnea, exercise intolerance, cough (sometimes described as "gagging"), anorexia, abdominal distention (ascites), and syncope (see Fig. 1-2). Loss of muscle mass (cardiac cachexia), accentuated along the dorsal midline, may be severe.

Physical examination findings vary with the degree of cardiac decompensation. Dogs with occult disease may have a normal physical exam. Others have a soft murmur of mitral or tricuspid regurgitation or an arrhythmia. Dogs with advanced disease and poor cardiac output have increased sympathetic tone and peripheral vasoconstriction. A consequence is mucous membrane pallor and slowed capillary refill time. The femoral arterial pulse and precordial impulse are often weak and rapid. Uncontrolled AF and frequent VPCs cause an irregular and usually rapid heart rhythm, with frequent pulse deficits and variable pulse strength (see Fig. 4-1). Signs of left- and/or right-sided CHF include tachypnea, increased breath sounds, pulmonary crackles, jugular venous distention or pulsations, pleural effusion or ascites, and/or hepatosplenomegaly. Heart sounds may be muffled in association with pleural effusion or poor cardiac contractility. An audible third heart sound (S<sub>3</sub> gallop) is a classic finding, although it may be obscured by an irregular heart rhythm. Systolic murmurs of mitral or tricuspid regurgitation that are soft to moderate in intensity are common.

# Diagnosis

#### RADIOGRAPHY

The stage of disease, chest conformation, and hydration status influence the radiographic findings. Generalized cardiomegaly is usually evident, although left heart enlargement may predominate (Fig. 7-1). In Doberman Pinschers the heart may appear minimally enlarged, except for the left atrium. In other dogs cardiomegaly may be severe and can mimic the globoid cardiac silhouette typical of large pericardial effusions. Distended pulmonary veins and pulmonary interstitial or alveolar opacities, especially in the hilar and dorsocaudal regions, accompany left heart failure with pulmonary edema. The distribution of pulmonary edema infiltrates may be asymmetric or widespread. Pleural effusion,

caudal vena cava distention, hepatomegaly, and ascites usually accompany right-sided CHF.

# **ELECTROCARDIOGRAPHY**

The electrocardiogram (ECG) findings in dogs with DCM are also variable. Sinus rhythm is usually the underlying

rhythm, although AF is often documented instead, especially in Great Danes and other giant breeds (see Fig. 2-11). Other atrial tachyarrhythmias, paroxysmal or sustained ventricular tachycardia, fusion complexes, and multiform VPCs are frequent findings. The QRS complexes may be tall (consistent with LV dilation), normal size, or small. Myocardial disease

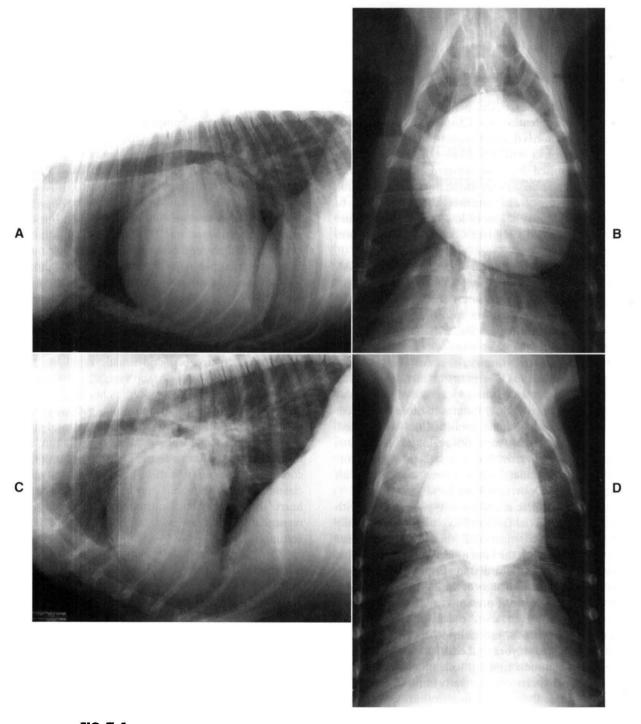


FIG 7-1

Radiographic examples of dilated cardiomyopathy in dogs. Lateral (A) and dorsoventral (B) views showing generalized cardiomegaly in a male Labrador Retriever. Note the cranial pulmonary vein is slightly larger than the accompanying artery in (A). Lateral (C) and dorsoventral (D) views of Doberman Pinscher depicting the prominent left atrial and relatively moderate ventricular enlargements commonly found in affected dogs of this breed. There is mild peribronchial pulmonary edema as well.

often causes a widened QRS complex with a slowed R-wave descent and slurred ST segment. A bundle-branch block pattern or other intraventricular conduction disturbance may be observed. The P waves in dogs with sinus rhythm are frequently widened and notched, suggesting LA enlargement.

Twenty-four-hour Holter monitoring is useful for documenting frequent ventricular ectopy. This has been used as a screening tool for cardiomyopathy in Doberman Pinschers and Boxers (see p. 135). The presence of >50 VPCs/day or any couplets or triplets is thought to predict future overt DCM in Doberman Pinschers. Nevertheless, some dogs with <50 VPCs/day on initial evaluation may develop DCM after several years. The frequency and complexity of ventricular tachyarrhythmias appear to be negatively correlated with fractional shortening; sustained ventricular tachycardia has been associated with increased risk of sudden death. Variability in the number of VPCs between repeated Holter recordings in the same dog can be high. If available, the technique of signal averaged electrocardiography can reveal the presence of ventricular late potentials, which may suggest an increased risk for sudden death in Doberman Pinschers with occult DCM.

#### **ECHOCARDIOGRAPHY**

Echocardiography is used to assess cardiac chamber dimensions and myocardial function and differentiate pericardial effusion or chronic valvular insufficiency from DCM. Dilated cardiac chambers and poor systolic ventricular wall and septal motion are characteristic findings in dogs with DCM. In severe cases only minimal wall motion is evident. All chambers are usually affected, but right atrial (RA) and right ventricular (RV) dimensions may appear normal, especially in Doberman Pinschers and Boxers. LV systolic (as well as diastolic) dimension is increased compared with normal ranges for the breed, and the ventricle appears more spherical. Fractional shortening and ejection fraction are decreased (Fig. 7-2). Other common features are a wide mitral valve E point-septal separation and reduced aortic root motion. LV free-wall and septal thicknesses are normal to decreased. The calculated end-systolic volume index (see p. 41) is generally over 80 ml/m<sup>2</sup> in dogs with overt DCM (<30 ml/m<sup>2</sup> is considered normal). Evidence for abnormal diastolic as well as systolic function can be found in dogs with advanced disease. Mild to moderate AV valve regurgitation is usually seen with Doppler echocardiography (Fig. 7-3).

Echocardiography is also used to screen for occult disease. There may be no clear abnormalities early in the disease. Alternatively, apparently healthy Doberman Pinschers may have slightly reduced fractional shortening compared with what is considered normal for other breeds. The following echocardiographic criteria appear to indicate high risk for overt DCM within 2 to 3 years in asymptomatic Doberman Pinschers: LVIDd >46 mm (in dogs <42 kg) or >50 mm (in dogs >42 kg), LVIDs >38 mm, or VPCs during initial examination, FS < 25%, and/or mitral valve E point–septal separation >8 mm (*LVID*, left ventricular internal diameter; *d*, diastole; *s*, systole).

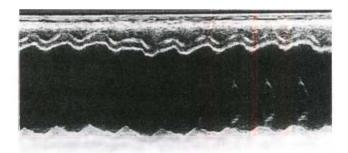


FIG 7-2
M-mode echocardiogram from a dog with dilated cardiomyopathy at the chordal (left side of figure) and mitral valve
(right side of figure) levels. Note attenuated wall motion
(fractional shortening = 18%) and the wide mitral valve E
point-septal separation (28 mm).

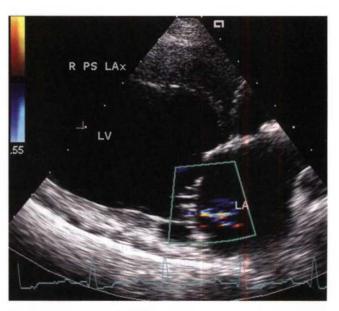


FIG 7-3
Mild mitral regurgitation is indicated by a relatively small area of disturbed flow in this systolic frame from a Standard Poodle with dilated cardiomyopathy. Note the LA and LV dilation. Right parasternal long axis view, optimized for the left ventricular inflow tract. LA, Left atrium; LV, left ventricle.

# **CLINICOPATHOLOGIC FINDINGS**

Clinicopathologic findings are noncontributory in most cases. In others, prerenal azotemia resulting from poor renal perfusion or mildly increased liver enzyme activities resulting from passive hepatic congestion occur. Severe CHF may be associated with hypoproteinemia, hyponatremia, and hyperkalemia. Hypothyroidism with associated hypercholesterolemia occurs in some dogs with DCM. Others have a reduced serum thyroid hormone concentration without hypothyroidism (sick euthyroid); normal TSH and free T<sub>4</sub> concentrations are common. Increased circulating neurohormones (e.g., norepiniphrine, aldosterone, endothelin, natriuretic peptides) occur mainly in DCM dogs with overt CHF. Natriuretic peptide elevations in dogs with occult DCM are also reported in some studies. Significant positive

correlations have been identified between LV dimensions (in both diastole and systole) and atrial natriuretic peptide, as well as endothelin (O'Sullivan et al., 2007). Neurohormonal changes in occult DCM were not associated with time to CHF onset or sudden death in this study; however, in dogs with overt CHF, increases in NE and endothelin over a month were inversely associated with survival time. Serum cardiac troponin (cTnT or cTnI) concentrations are elevated in some dogs with DCM, as well as with other causes of myocyte injury.

#### Treatment

# OCCULT DILATED CARDIOMYOPATHY

Dogs with LV dilation or reduced FS are often treated with an angiotensin-converting enzyme inhibitor (ACEI), although it is unclear whether this prolongs the preclinical phase. Other therapy aimed at modulating early neurohormonal responses and ventricular remodeling processes have theoretical appeal, but their clinical usefulness is not clear. Further study of this using certain  $\beta$ -blockers (e.g., carvedilol, metoprolol), spironolactone, pimobendan, and other agents is ongoing.

The decision to use antiarrhythmic drug therapy in dogs with ventricular tachyarrhythmias is influenced by whether they result in clinical signs (e.g., episodic weakness, syncope) as well as the arrhythmia frequency and complexity seen on Holter recording. Various antiarrhythmic agents have been used, but the most effective regimen(s) and when to institute therapy are still not clear. It would seem that a regimen that increases ventricular fibrillation threshold and decreases arrhythmia frequency and severity is desired. Sotalol, amiodarone (both Class III agents), as well as the combination of mexiletine and atenolol or procainamide with atenolol, may be useful.

# CLINICALLY EVIDENT DILATED CARDIOMYOPATHY

Therapy is aimed at improving the animal's quality of life and prolonging survival to the extent possible by controlling CHF signs, optimizing cardiac output, and managing arrhythmias. Pimobendan (or digoxin), an ACEI, and furosemide are used for most dogs (Box 7-1). Severe heart failure may require additional therapy, including an intravenous (IV) inotropic agent. Antiarrhythmic drugs are used on the basis of individual need.

Dogs with acute CHF are treated as outlined in Box 3-1, with parenteral furosemide, supplemental oxygen, 2% nitroglycerin ointment or sodium nitroprusside infusion, inotropic support, and cage rest, with or without aminophylline and morphine or butorphanol. Thoracocentesis is indicated if pleural effusion is suspected or identified.

Inotropic support can be in the form of oral pimobendan and/or digoxin if oral administration is not overly stressful and the delay in onset of effects is not critical. More acute and stronger inotropic support for dogs with very poor contractility, persistent hypotension, or fulminant CHF can be



Treatment Outline for Dogs with Dilated Cardiomyopathy

#### Mild to Moderate Signs of Congestive Heart Failure\*

ACEI

Furosemide

Pimobendan (or digoxin)

Antiarrhythmic therapy, if necessary

+/- Initiate spironolactone

Complete exercise restriction until signs abate

Moderate dietary salt restriction

#### Severe, Acute Signs of Congestive Heart Failure\*

Supplemental O<sub>2</sub>

Furosemide (parenteral)

Inotropic support (e.g., IV dobutamine and/or amrinone with minimal fluid volume; initiate oral pimobendan [or digoxin] when possible)

ACEI as soon as possible

Other vasodilator with caution (e.g., IV nitroprusside, oral hydralazine, or amlodipine with topical nitroglycerine)

Antiarrhythmic therapy, if necessary\*\* (With uncontrolled AF, catecholamine infusion can further increase AV conduction and ventricular response rate; if dopamine or dobutamine is necessary, use IV diltiazem or digoxin [either by oral route or cautious IV loading])

+/- Bronchodilator

+/- Butorphanol or morphine

Cage rest

Minimize patient handling

Monitor respiratory rate, heart rate and rhythm, arterial blood pressure, peripheral perfusion, urine output, renal function, serum electrolytes, etc.

#### AF and Inadequate Heart Rate Control with Digoxin\*\*

Acute: add IV diltiazem

Chronic: add oral β-blocker at low dose or diltiazem; titrate to effect

#### Chronic Dilated Cardiomyopathy Management\*

ACE

Furosemide (lowest effective dosage and frequency)

Pimobendan/digoxin

Spironolactone

Antiarrhythmic therapy as indicated

+/- Other medications (see p. 67)

+/- Carvedilol/metoprolol

Client education

Resting respiratory rate (and heart rate if possible) monitoring at home

Regular but mild exercise

Dietary salt restriction

Routine health maintenance (including heartworm testing and prophylaxis in endemic areas)

Proper management of other medical problems

ACEI, Angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AV, atrioventricular.

<sup>\*</sup> See text and Chapter 3 for further details.

<sup>\*\*</sup>See Chapter 4, p. 81.

provided by IV infusion of dobutamine or dopamine for 2 (to 3) days. The phosphodiesterase inhibitors amrinone and milrinone may be helpful for short-term stabilization in some dogs and can be used concurrently with digoxin and a catecholamine. Long-term use of strong positive inotropic drugs is thought to have detrimental effects on the myocardium. During infusion of these drugs, the animal must be observed closely for worsening tachycardia or arrhythmias (especially VPCs).

If arrhythmias develop, the drug is discontinued or infused at up to half the original rate. In dogs with AF, catecholamine infusion is likely to increase the ventricular response rate because the drug enhances AV conduction. If dopamine or dobutamine is thought necessary in dogs with AF, rapid oral or cautious IV diltiazem can be used to slow AV conduction. Digoxin, either administered orally or by cautious IV loading doses, is an alternative.

Because clinical status may deteriorate rapidly, frequent patient evaluation is important. Respiratory rate and character, lung sounds, pulse quality, heart rate and rhythm, peripheral perfusion, rectal temperature, hydration status, body weight, renal function, mentation, pulse oxymetry, and blood pressure should be monitored. Ventricular contractility is abysmal in many dogs with severe DCM; because these patients have little cardiac reserve, diuretic and vasodilator therapy may lead to hypotension, and even cardiogenic shock.

# Long-Term Therapy

Chronic inotropic therapy for dogs with DCM traditionally consisted of oral digoxin, but pimobendan now offers several advantages over digoxin (see p. 65). Pimobendan (Vetmedin, Boehringer Ingelheim) is a phosphodiesterase III inhibitor that increases contractility through a Ca<sup>++</sup>-sensitizing effect; the drug also has vasodilator and other beneficial effects. Digoxin, with its neurohormonal modulating and antiarrhythmic effects, may still be useful and can be given with pimobendan. Digoxin is indicated in dogs with AF to help slow the ventricular response rate. It can also suppress some other supraventricular tachyarrhythmias.

If digoxin is used, it is generally initiated with oral maintenance doses. Toxicity seems to develop at relatively low dosages in some dogs, especially Doberman Pinschers. A total maximum daily dose of 0.5 mg is generally used for large and giant-breed dogs, except for Doberman Pinschers, which are given a total maximum dose of 0.25 mg/day to 0.375 mg/day. Serum digoxin concentration should be measured 7 to 10 days after digoxin therapy is initiated or the dose is changed (see p. 66). Dogs with AF and a ventricular rate exceeding 200 beats/min can be cautiously given digoxin IV (see Box 3-1) or twice the oral maintenance dose on the first day to more rapidly achieve effective blood concentrations. However, the use of IV or rapid oral diltiazem is probably safer (see p. 81). If oral digoxin alone has not significantly reduced the heart rate after 36 to 48 hours, a β-blocker or diltiazem may be added (see Table 4-2). Because these agents can have negative inotropic effects, a low initial dose and gradual dosage titration to effect or a maximum recommended level is advised. Heart rate control in dogs with AF is important. A maximum ventricular rate of 140 to 150 beats/min in the hospital (i.e., stressful) setting is the recommended target; lower heart rates (c.g., ~100 beats/min or less) are expected at home. Because accurate counting of heart rate by auscultation or chest palpation in dogs with AF is difficult, an ECG recording is recommended. Femoral pulses should not be used to assess heart rate in the presence of AF.

Furosemide is used at the lowest effective oral dose and at consistent time intervals for long-term therapy (see Table 3-3). Hypokalemia and alkalosis are uncommon sequelae, unless anorexia or vomiting occurs. Potassium supplements may be given if hypokalemia is documented. However, these should be used cautiously if an ACEI and/or spironolactone (see Table 3-3 and p. 62) are also being administered to prevent hyperkalemia, especially if renal disease is present.

Spironolactone is thought to be useful for chronic therapy because of its aldosterone-antagonist, as well as potential diuretic, effects. Increased aldosterone production develops as a component of neurohormonal activation in heart failure, but ACEIs do not fully suppress this. Aldosterone is known to promote cardiovascular fibrosis and abnormal remodeling and as such contributes to the progression of cardiac disease. Therefore spironolactone is advocated as adjunctive therapy in combination with an ACEI, furosemide, and pimobendan/digoxin for chronic DCM therapy.

An ACEI should be used in the chronic treatment of DCM. Angiotensin-converting enzyme inhibition can attenuate progressive ventricular dilation and secondary mitral regurgitation. ACEIs have a positive effect on survival in both people and dogs with myocardial failure. These drugs minimize clinical signs and increase exercise tolerance. Enalapril or benazepril are used most extensively, but other ACEIs have similar effects.

The pure arteriolar dilator hydralazine can also improve cardiac output and exercise tolerance, as well as help reduce congestion; however, it can precipitate hypotension and reflex tachycardia, and it tends to exacerbate neurohormonal activation. Hydralazine can be used in combination with a nitrate in dogs that do not tolerate an ACEI. Hydralazine or amlodipine (see Table 3-3) could also be useful as adjunct therapy for dogs with refractory CHF, although arterial blood pressure should be carefully monitored in such animals. Any vasodilator must be used cautiously in dogs with a low cardiac reserve because of the increased potential for hypotension. Therapy is initiated at a low dose; if this is well-tolerated, the next dose is increased to a low maintenance level. The patient should be evaluated for several hours after each incremental dose, ideally by blood pressure measurement. Signs of worsening tachycardia, weakened pulses, or lethargy also can indicate the presence of hypotension. The jugular venous PO2 can be used to estimate directional changes in cardiac output; a venous PO<sub>2</sub> >30 mm Hg is desirable.

A number of other therapies may be useful in certain dogs with DCM, although additional studies are needed to define optimal recommendations. These include omega-3 fatty acids, L-carnitine (in dogs with low myocardial carnitine concentrations), taurine (in dogs with low plasma concentrations), long-term  $\beta$ -blocker therapy (e.g., carvedilol or metoprolol), and possibly others (see Chapter 3, p. 69). Several palliative surgical therapies for DCM have been described in dogs but are not widely used.

# Monitoring

Many dogs can be maintained fairly well for a variable time with chronic oral therapy. Owner education regarding the purpose, dosage, and adverse effects of each drug used is also important. Monitoring the dog's resting respiratory (and heart) rate at home helps assess how well the patient's CHF is controlled. Periodic reevaluation is important, but the time frame depends on the animal's status. Visits once or twice a week may be needed initially. Dogs with stable heart failure can be rechecked every 2 or 3 months. Serum electrolyte and creatinine (or BUN) concentrations, an ECG, pulmonary status, blood pressure, serum digoxin concentration, body weight, and other appropriate factors can be evaluated, and therapy adjusted as needed.

# **Prognosis**

The prognosis for dogs with DCM is generally guarded to poor. Historically, most dogs do not survive longer than 3 months after the clinical manifestations of CHF, although approximately 25% to 40% of affected dogs live longer than 6 months if initial response to therapy is good. The probability of survival for 2 years is estimated at 7.5% to 28%. However, the advent of newer therapies may change this bleak picture. Pleural effusion and possibly ascites and pulmonary edema have been identified as independent indicators of poorer prognosis.

Sudden death may occur even in the occult stage, before heart failure is apparent. Sudden death occurs in about 20% to 40% of affected Doberman Pinschers. Although ventricular tachyarrhythmias are thought to precipitate cardiac arrest most commonly, bradyarrhythmias may be involved in some dogs.

Doberman Pinschers with occult DCM often experience deterioration within 6 to 12 months. Dobermans in overt CHF when initially presented generally do not live long, with a reported median survival of less than 7 weeks. The prognosis is worse if AF is present in dogs with CHF. Most symptomatic dogs are between 5 and 10 years old at the time of death.

In each case, however, it is reasonable to assess the animal's response to initial treatment before pronouncing an unequivocally dismal prognosis. Early diagnosis may help prolong life; further cardiac evaluation is indicated for dogs with a history of reduced exercise tolerance, weakness, or syncope or in those in which an arrhythmia, murmur, or gallop sound is detected.

# ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

# CARDIOMYOPATHY IN BOXERS

Myocardial disease in Boxers has similar features to those of people with ARVC. Histologic changes in the myocardium are more extensive than those in dogs of other breeds with cardiomyopathy and include atrophy of myofibers, fibrosis, and fatty infiltration. Focal areas of myocytolysis, necrosis, hemorrhage, and mononuclear cell infiltration are also common.

Although clinical features vary, the prevalence of ventricular arrhythmias and syncope is high in Boxers with myocardial disease. A genetic basis is believed to exist given that the disease is more prevalent in some bloodlines. Three disease categories have been described. The first consists of dogs with ventricular tachyarrhythmia but without clinical signs. The second consists of dogs that have syncope or weakness associated with paroxysmal or sustained ventricular tachycardia, despite normal heart size and LV function. The third group comprises Boxers with poor myocardial function and CHF, as well as ventricular tachyarrhythmias. Dogs with mild echocardiographic changes and those with syncope or weakness may later develop poor LV function and CHF. There appears to be geographical variation in the prevalence of these clinical presentations; for example, tachyarrhythmias with normal LV function are typical in affected U.S. Boxers, whereas I.V dysfunction appears to be more common in parts of Europe.

## Clinical Findings

Signs may appear at any age, but the mean age is reportedly 8.5 years (range <1-15 years). The most consistent clinical finding is a cardiac arrhythmia. When CHF occurs, left-sided signs are more common than ascites or other signs of right-sided heart failure. Many Boxers also develop a mitral insufficiency murmur.

The radiographic findings are variable; many Boxers have no visible abnormalities. Those with congestive signs generally show evidence of cardiomegaly and pulmonary edema. Echocardiographic findings also vary. Many Boxers have normal cardiac size and function; others show chamber dilation with reduced fractional shortening.

The characteristic ECG finding is ventricular ectopy. VPCs occur singly, in pairs, in short runs, or as sustained ventricular tachycardia. Most ectopic ventricular complexes appear upright in leads II and aVF. Some Boxers have multiform VPCs. There usually is an underlying sinus rhythm. AF is less common. Supraventricular tachycardia, conduction abnormalities, and evidence of chamber enlargement also are sometimes seen on ECG.

Twenty-four-hour Holter monitoring is often used as a screening tool for Boxer ARVC. It also is recommended to evaluate the efficacy of antiarrhythmic drug therapy. Frequent VPCs and/or complex ventricular arrhythmias are characteristic findings in affected dogs. However, an absolute number of VPCs/24-hour period that might separate normal from abnormal dogs is not (and may never be) clear. An

arbitrary cut-off of >50 VPCs/24-hour period is often used to designate an abnormal frequency. However, there can be enormous variability in the number of VPCs between repeated Holter recordings in the same dog. Very frequent VPCs or episodes of ventricular tachycardia are thought to signal an increased risk for syncope and sudden death.

#### **Treatment**

Boxers with signs from tachyarrhythmias, but with normal heart size and LV function, are treated with antiarrhythmic drugs. Some asymptomatic dogs found to have ventricular tachycardia on Holter monitoring are also given an antiarrhythmic drug. The best regimen(s) and when to institute therapy are still not clear. Antiarrhythmic drug therapy that is apparently successful in reducing VPC number based on Holter recording may still not prevent sudden death. Sotalol, mexiletine with atenolol, amiodarone, or procainamide with atenolol have been advocated (see Chapter 4) because they might reduce the risk for sudden death from ventricular fibrillation, but further study is needed. Some dogs require treatment for persistent supraventricular tachyarrhythmias.

Therapy for CHF is similar to that described for dogs with idiopathic DCM. Myocardial carnitine deficiency has been documented in some Boxers with DCM and heart failure. Some of these dogs have responded to oral L-carnitine supplementation. Digoxin is used sparingly, if at all, when ventricular tachyarrhythmias are frequent.

# **Prognosis**

The prognosis for affected Boxers is guarded. Survival is often <6 months in those with CHF. Asymptomatic dogs may have a more optimistic future, but the likelihood of developing serious arrhythmias is high. Sudden death is common, presumably from VPCs leading to ventricular fibrillation. The ventricular tachyarrhythmias may be refractory to drug therapy. Furthermore, even if most arrhythmias are suppressed, an increased survival is not assured.

# ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN NONBOXER DOGS

A form of cardiomyopathy that mainly affects the right ventricle has been observed rarely in dogs. It appears similar to ARVC described in people and cats (see p. 154). Pathologic changes are characterized by widespread fibrous and fatty tissue replacement in the RV myocardium. In certain geographical areas, trypanosomiasis is a possible differential diagnosis. Clinical manifestations are largely related to right-sided CHF and severe ventricular tachyarrhythmias. Marked right heart dilation is typical. Sudden death is a common outcome in people with ARVC.

# SECONDARY MYOCARDIAL DISEASE

Poor myocardial function may result from a variety of identifiable insults and nutritional deficiencies. Myocardial infec-

tions (see p. 137), inflammation, trauma (see p. 139), ischemia, neoplastic infiltrations, and metabolic abnormalities can impair normal contractile function. Hyperthermia, irradiation, electric shock, and other insults can also damage the myocardium. Some substances are known cardiac toxins.

# MYOCARDIAL TOXINS Doxorubicin

The antineoplastic drug doxorubicin induces both acute and chronic cardiotoxicity. Histamine, secondary catecholamine release, and free-radical production appear to be involved in the pathogenesis of myocardial damage, which leads to decreased cardiac output, arrhythmias, and degeneration of myocytes. Doxorubicin-induced cardiotoxicity is directly related to the peak serum concentration of the drug; administering the drug diluted (0.5 mg/ml) over 20 to 40 minutes minimizes the risk of developing cardiotoxicity. Progressive myocardial damage and fibrosis have developed in association with cumulative doses of >160 mg/m<sup>2</sup> and sometimes as low as 100 mg/m<sup>2</sup>. In dogs that have normal pretreatment cardiac function, clinical cardiotoxicity is uncommon until the cumulative dose exceeds 240 mg/m<sup>2</sup>. It is difficult to predict whether and when clinical cardiotoxicity will occur. Increases in circulating cardiac troponin concentrations can be seen, but more work is needed to clarify the utility of this in monitoring dogs for doxorubicin-induced myocardial injury.

Cardiac conduction defects (infranodal AV block and bundle branch block) as well as ventricular and supraventricular tachyarrhythmias can develop in affected dogs. ECG changes do not necessarily precede clinical heart failure. Dogs with underlying cardiac abnormalities and those of breeds with a higher prevalence of idiopathic DCM are thought to be at greater risk for doxorubicin-induced cardiotoxicity. Recently, carvedilol has been shown to minimize or prevent the development of doxorubicin-induced cardiotoxicity in humans; we have had similar anecdotal experiences in dogs. Clinical features of this cardiomyopathy are similar to those of idiopathic DCM.

#### **Other Toxins**

Ethyl alcohol, especially if given intravenously for the treatment of ethylene glycol intoxication, can cause severe myocardial depression and death; slow administration of a diluted (20% or less) solution is advised. Other cardiac toxins include plant toxins (e.g., *Taxus*, foxglove, black locust, buttercups, lily-of-the-valley, gossypol), cocaine, anesthetic drugs, cobalt, catecholamines, and ionophores such as monensin.

# METABOLIC AND NUTRITIONAL DEFICIENCY L-carnitine

L-carnitine is an essential component of the mitochondrial membrane transport system for fatty acids, which are the heart's most important energy source. It also transports potentially toxic metabolites out of the mitochondria in the form of carnitine esters. L-carnitine—linked defects in myocardial metabolism have been found in some dogs with DCM. Rather than simple L-carnitine deficiency, one or more underlying genetic or acquired metabolic defects are suspected. There may be an association between DCM and carnitine deficiency in some families of Boxers, Doberman Pinschers, Great Danes, Irish Wolfhounds, Newfoundlands, and Cocker Spaniels. L-carnitine is mainly present in foods of animal origin. DCM has developed in some dogs fed strict vegetarian diets.

Plasma carnitine concentration is not a sensitive indicator of myocardial carnitine deficiency. Most dogs with myocardial carnitine deficiency, diagnosed via endomyocardial biopsy, have had normal or high plasma carnitine concentrations. Furthermore, the response to oral carnitine supplementation is inconsistent. Subjective improvement may occur, but few dogs have echocardiographic evidence of improved function. Dogs that do respond show clinical improvement within the first month of supplementation; there may be some degree of improvement in echo parameters after 2 to 3 months. L-carnitine supplementation does not suppress preexisting arrhythmias or prevent sudden death. See p. 69 for supplementation guidelines.

#### **Taurine**

Although most dogs with DCM are not taurine deficient, low plasma taurine concentration is found in some. Low taurine, and sometimes carnitine, concentrations occur in Cocker Spaniels with DCM. Oral supplementation of these amino acids can improve LV size and function as well as reduce the need for heart failure medications in this breed. Low plasma taurine concentrations have also been found in some Golden Retrievers, Labrador Retrievers, Saint Bernards, Dalmatians, and other dogs with DCM. A normally adequate taurine content is found in the diets of some such cases, although others have been fed low-protein or vegetarian diets. The role of taurine supplementation is unclear. Although taurinedeficient dogs may show some echocardiographic improvement after supplementation, there is questionable effect on survival time. Nevertheless, measurement of plasma taurine or a trial of supplemental taurine for at least 4 months may be useful, especially in an atypical breed affected with DCM. (See p. 69 for supplementation guidelines.) Plasma taurine concentrations <25 (to 40) nmol/ml and blood taurine concentrations <200 (or 150) nmol/ml are generally considered deficient. Specific collection and submission guidelines should be obtained from the laboratory used.

#### Other Factors

Myocardial injury induced by free radicals may play a role in a number of diseases. Evidence for increased oxidative stress has been found in dogs with CHF and myocardial failure, but the clinical ramifications of this are unclear. Diseases such as hypothyroidism, pheochromocytoma, and diabetes mellitus have been associated with reduced myocardial function, but clinical heart failure is unusual in dogs secondary to these conditions alone. Excessive sympathetic stimulation stemming from brain or spinal cord injury results in myocardial hemorrhage, necrosis, and arrhythmias (brain-heart syndrome). Muscular dystrophy of the fasciohumoral type (reported in English Springer Spaniels) may result in atrial standstill and heart failure. Canine X-linked (Duchenne's) muscular dystrophy in Golden Retrievers and other breeds also has been associated with myocardial fibrosis and mineralization. Rarely, nonneoplastic (e.g., glycogen storage disease) and neoplastic (metastatic and primary) infiltrates interfere with normal myocardial function. Immunologic mechanisms may also play an important role in the pathogenesis of myocardial dysfunction in some dogs with myocarditis.

# ISCHEMIC MYOCARDIAL DISEASE

Acute myocardial infarction resulting from coronary embolization is uncommon. An underlying disease associated with increased risk for thromboembolism, such as bacterial endocarditis, neoplasia, severe renal disease, immune-mediated hemolytic anemia, acute pancreatitis, disseminated intravascular coagulopathy, and/or corticosteroid use, underlies most cases. Sporadic reports of myocardial infarction are associated with congenital ventricular outflow obstruction, patent ductus arteriosus, hypertrophic cardiomyopathy, and mitral insufficiency. Atherosclerosis of the major coronary arteries, which can accompany severe hypothyroidism in dogs, rarely leads to acute myocardial infarction. Clinical signs of acute major coronary artery obstruction are likely to include arrhythmias, pulmonary edema, marked ST segment change on ECG, and evidence of regional or global myocardial contractile dysfunction on echocardiogram. High circulating cardiac troponin concentrations and possibly creatine kinase activity occur after myocardial injury and necrosis.

Disease of small coronary vessels is recognized as well. Non-atherosclerotic narrowing of small coronary arteries could be more clinically important than previously assumed. Hyalinization of small coronary vessels and intramural myocardial infarctions have been described in dogs with chronic degenerative AV valve disease, but they can occur in older dogs without valve disease as well. Fibromuscular arteriosclerosis of small coronary vessels is also described. These changes in the walls of the small coronary arteries cause luminal narrowing and can impair resting coronary blood flow as well as vasodilatory responses. Small myocardial infarctions and secondary fibrosis lead to reduced myocardial function. Various arrhythmias can occur. Eventual CHF is a cause of death in many cases with intramural coronary arteriosclerosis. Sudden death is a less common sequela. Larger breeds of dog may be predisposed, although Cocker Spaniels and Cavalier King Charles Spaniels appear to be commonly affected smaller breeds.

# TACHYCARDIA-INDUCED CARDIOMYOPATHY

The term tachycardia induced cardiomyopathy (TICM) refers to the progressive myocardial dysfunction, activation of neurohormonal compensatory mechanisms, and CHF that result from rapid, incessant tachycardias. The myocardial failure may be reversible if the heart rate can be normalized in time. TICM has been described in several dogs with AV nodal reciprocating tachycardias associated with accessory conduction pathways that bypass the AV node (e.g., Wolff-Parkinson-White; see p. 27). Rapid artificial pacing (e.g., >200 beats/min) is a common model for inducing experimental myocardial failure that simulates DCM.

#### HYPERTROPHIC CARDIOMYOPATHY

In contrast to cats, hypertrophic cardiomyopathy (HCM) is quite uncommon in dogs. A genetic basis is suspected, although the cause is unknown. It is possible that several disease processes lead to similar ventricular changes. The pathophysiology is similar to that of HCM in cats (see Chapter 8). Abnormal, excessive myocardial hypertrophy increases ventricular stiffness and leads to diastolic dysfunction. The IV hypertrophy is usually symmetric, but regional variation in wall or septal thickness can occur. Compromised coronary perfusion is likely with severe ventricular hypertrophy. This leads to myocardial ischemia, which exacerbates arrhythmias, delays ventricular relaxation, and further impairs filling. High LV filling pressure predisposes to pulmonary venous congestion and edema. Besides diastolic dysfunction, systolic dynamic LV outflow obstruction occurs in some dogs. Malposition of the mitral apparatus may contribute to systolic anterior mitral valve motion and IV outflow obstruction as well as to mitral regurgitation. In some dogs asymmetric septal hypertrophy also contributes to outflow obstruction. IV outflow obstruction increases ventricular wall stress and myocardial oxygen requirement while also impairing coronary blood flow. Heart rate elevations magnify these abnormalities.

#### **Clinical Features**

HCM is most commonly diagnosed in young to middle-age large-breed dogs, although there is a wide age distribution. Various breeds are affected. There may be a higher prevalence of HCM in males. Clinical signs of CHF, episodic weakness, and/or syncope occur in some dogs. Sudden death is the only sign in some cases. Ventricular arrhythmias secondary to myocardial ischemia are presumed to cause the low-output signs and sudden death. A systolic murmur, related to either LV outflow obstruction or mitral insufficiency, may be heard on auscultation. The systolic ejection murmur of ventricular outflow obstruction becomes louder when ventricular contractility is increased (e.g., with exercise or excitement) or when afterload is reduced (e.g., from vasodilator use). An S<sub>4</sub> gallop sound is heard in some affected dogs.

# **Diagnosis**

Echocardiography is the best diagnostic tool for HCM. An abnormally thick left ventricle, with or without narrowing of the LV outflow tract area or asymmetrical septal hypertrophy, and LA enlargement are characteristic findings. Mitral regurgitation may be evident on Doppler studies. Systolic anterior motion of the mitral valve may result from

dynamic outflow obstruction causes. Partial systolic aortic valve closure may be seen as well. Other causes of LV hypertrophy include congenital subaortic stenosis, hypertensive renal disease, thyrotoxicosis, and pheochromocytoma. Thoracic radiographs may indicate LA and LV enlargement, with or without pulmonary congestion or edema. Some cases appear radiographically normal. ECG findings may include ventricular tachyarrhythmias and conduction abnormalities, such as complete heart block, first-degree AV block, and fascicular blocks. Criteria for LV enlargement are variably present.

#### **Treatment**

The general goals of HCM treatment are to enhance myocardial relaxation and ventricular filling, control pulmonary edema, and suppress arrhythmias. A β-blocker (see p. 89) or Ca++-channel blocker (see p. 91) may lower heart rate, prolong ventricular filling time, reduce ventricular contractility, and minimize myocardial oxygen requirement. βblockers can also reduce dynamic LV outflow obstruction and may suppress arrhythmias induced by heightened sympathetic activity, whereas Ca't-blockers may facilitate myocardial relaxation. Diltiazem has a lesser inotropic effect and would be less useful against dynamic outflow obstruction, especially in view of its vasodilating effect. Because β- and Ca++-channel blockers can worsen AV conduction abnormalities, they may be relatively contraindicated in certain animals. A diuretic and ACEI are indicated if congestive signs are present. Digoxin should not be used because it may increase myocardial oxygen requirements, worsen outflow obstruction, and predispose to the development of ventricular arrhythmias. Exercise restriction is advised in dogs with HCM.

#### **MYOCARDITIS**

A wide variety of agents can affect the myocardium, although disease manifestations in other organ systems may overshadow the cardiac involvement. The heart can be injured by direct invasion of the infective agent, by toxins it elaborates, or by the host's immune response. Non-infective causes of myocarditis include cardiotoxic drugs and drug hypersensitivity reactions. Myocarditis can cause persistent cardiac arrhythmias and progressively impair myocardial function.

# INFECTIVE MYOCARDITIS

# Etiology and Pathophysiology Viral Myocarditis

Lymphocytic myocarditis has been associated with acute viral infections in experimental animals and in people. Cardiotropic viruses can play an important role in the pathogenesis of myocarditis and subsequent cardiomyopathy in several species, but this is not recognized commonly in dogs. The host animal's immune responses to viral and nonviral antigens contribute to myocardial inflammation and damage.

A syndrome of parvoviral myocarditis was well-known in the late 1970s and early 1980s. It is characterized by a peracute necrotizing myocarditis and sudden death (with or without signs of acute respiratory distress) in apparently healthy puppies about 4 to 8 weeks old. Cardiac dilation with pale streaks in the myocardium, gross evidence of congestive failure, large basophilic or amorphophilic intranuclear inclusion bodies, myocyte degeneration, and focal mononuclear cell infiltrates are typical necropsy findings. This syndrome is uncommon now, probably as a result of maternal antibody production in response to virus exposure and vaccination. Parvovirus may cause a form of DCM in young dogs that survive neonatal infection; viral genetic material has been identified in some canine ventricular myocardial samples in the absence of classic intranuclear inclusion bodies.

Canine distemper virus may cause myocarditis in young puppies, but multisystemic signs usually predominate. Histologic changes in the myocardium are mild compared with those in the classic form of parvovirus myocarditis. Experimental herpesvirus infection of pups during gestation also causes necrotizing myocarditis with intranuclear inclusion bodies leading to fetal or perinatal death.

# **Bacterial Myocarditis**

Bacteremia and bacterial endocarditis or pericarditis can cause focal or multifocal suppurative myocardial inflammation or abscess formation. Localized infections elsewhere in the body may be the source of the organisms. Clinical signs include malaise; weight loss; and, inconsistently, fever. Arrhythmias and cardiac conduction abnormalities are common, but murmurs are rare unless concurrent valvular endocarditis or another underlying cardiac defect is present. Serial bacterial (or fungal) blood cultures, serology, or PCR may allow identification of the organism. *Bartonella vinsonii* subspecies have been associated with cardiac arrhythmias, myocarditis, endocarditis, and sudden death.

# **Lyme Carditis**

Lyme disease is more prevalent in certain geographic areas, especially the northeastern, western coastal, and north central United States, as well as in Japan and Europe, among other areas. The spirochete Borrelia burgdorferi (or related species) is transmitted to dogs by ticks (especially Ixodes genus) and possibly other biting insects. Third-degree (complete) and high-grade second-degree AV block have been identified in dogs with Lyme disease. Syncope, CHF, reduced myocardial contractility, and ventricular arrhythmias also are reported in affected dogs. Pathologic findings of Lyme myocarditis include infiltrates of plasma cells, macrophages, neutrophils, and lymphocytes, with areas of myocardial necrosis. These are similar to findings in human Lyme carditis. A presumptive diagnosis is made on the basis of the finding of positive (or increasing) serum titers or a positive SNAP test and concurrent signs of myocarditis, with or without other systemic signs. The findings from endomyocardial biopsy, if available, may be helpful in confirming the diagnosis. Treatment with an appropriate antibiotic should be instituted pending diagnostic test results. Cardiac drugs are used as needed. Resolution of AV conduction block may not occur in dogs despite appropriate antimicrobial therapy.

# **Protozoal Myocarditis**

Trypanosoma cruzi, Toxoplasma gondii, Neosporum caninum, Babesia canis, and Hepatozoon canis are known to affect the myocardium. Trypanosomiasis (Chagas' disease) has occurred mainly in young dogs in Texas, Louisiana, Oklahoma, Virginia, and other southern states in the United States. The possibility for human infection should be recognized; this is an important cause of human myocarditis and subsequent cardiomyopathy in Central and South America. The organism is transmitted by bloodsucking insects of the family Reduviidae and is enzootic in wild animals of the region. Amastigotes of T. cruzi cause myocarditis with a mononuclear cell infiltrate and disruption and necrosis of myocardial fibers. Acute, latent, and chronic phases of Chagas' myocarditis have been described. Lethargy, depression, and other systemic signs, as well as various tachyarrhythmias, AV conduction defects, and sudden death, are seen in dogs with acute trypanosomiasis. Clinical signs are sometimes subtle. The disease is diagnosed in the acute stage by finding trypomastigotes in thick peripheral blood smears; the organism can be isolated in cell culture or by inoculation into mice. Animals that survive the acute phase enter a latent phase of variable duration. During this phase the parasitemia is resolved, and antibodies develop against the organism as well as cardiac antigens. Chronic Chagas' disease is characterized by progressive right-sided or generalized cardiomegaly and various arrhythmias. Ventricular tachvarrhythmias are most common, but supraventricular tachyarrhythmias may occur. Right bundle branch block and AV conduction disturbances are also reported. Ventricular dilation and reduced myocardial function are usually evident echocardiographically. Clinical signs of biventricular failure are common. Antemortem diagnosis in chronic cases may be possible through serologic testing. Therapy in the acute stage is aimed at eliminating the organism and minimizing myocardial inflammation; several treatments have been tried with variable success. The therapy for chronic Chagas' disease is aimed at supporting myocardial function, controlling congestive signs, and suppressing arrhythmias.

Toxoplasmosis and neosporiosis can cause clinical myocarditis in conjunction with generalized systemic infection, especially in the immunocompromised animal. The organism becomes encysted in the heart and various other body tissues after the initial infection. With rupture of these cysts, expelled bradyzoites induce hypersensitivity reactions and tissue necrosis. Other systemic signs often overshadow signs of myocarditis. Immunosuppressed dogs with chronic toxoplasmosis (or neosporiosis) may be prone to active disease, including clinically relevant myocarditis, pneumonia, chorioretinitis, and encephalitis. Antiprotozoal therapy may be successful. Babesiosis can be associated with cardiac lesions in dogs, including myocardial hemorrhage, inflammation, and necrosis. Pericardial effusion and variable ECG changes are also noted in some cases. A correlation between plasma cardiac troponin I (cTnI) concentration and clinical severity, survival, and cardiac histopathologic findings was shown in dogs with babesiosis.

*H. canis* may involve the myocardium during part of its life cycle; this was found in dogs along the Texas coast. Infection occurs as a result of ingesting the organism's definitive host, the brown dog tick (*Rhipicephalus sanguineus*). Clinical signs include stiffness, anorexia, fever, neutrophilia, and periosteal new bone reaction.

#### Other Causes

Rarely, fungi (Aspergillus, Cryptococcus, Coccidioides, Histoplasma, Paecilomyces), rickettsiae (Rickettsia rickettsii, Ehrlichia canis, Bartonella elizabethae), algaelike organisms (Prototheca sp.), and nematode larval migration (Toxocara sp.) cause myocarditis. Affected animals are usually immunosuppressed and have systemic signs of disease. Rocky Mountain spotted fever (R. rickettsii) occasionally causes fatal ventricular arrhythmias, along with necrotizing vasculitis, myocardial thrombosis, and ischemia. Angiostrongylus vasorum infection in association with immune-mediated thrombocytopenia has rarely caused myocarditis, thrombosing arteritis, and sudden death.

# **Clinical Findings and Diagnosis**

Unexplained onset of arrhythmias or heart failure after a recent episode of infective disease or drug exposure is the classic clinical presentation of acute myocarditis. However, definitive diagnosis is difficult because clinical and clinicopathologic findings are usually nonspecific and inconsistent. A database including complete blood count, serum biochemical profile with creatine kinase activity, cardiac troponin concentration, thoracic and abdominal radiographs, and urinalysis are usually obtained. ECG changes could include an ST segment shift, T-wave or QRS voltage changes, AV conduction abnormalities, and various arrhythmias. Echocardiographic signs of poor regional or global wall motion, altered myocardial echogenicity, or pericardial effusion may be evident. In dogs with persistent fever, serial bacterial (or fungal) blood cultures may be useful. Serologic screening for known infective causes may or may not be helpful. Histologic criteria for a diagnosis of myocarditis include inflammatory infiltrates with myocyte degeneration and necrosis. Endomyocardial biopsy specimens are currently the only means of obtaining a definitive antemortem diagnosis, but if the lesions are focal, the findings may not be diagnostic.

## **Treatment**

Unless a specific etiology can be identified and treated, therapy for suspected myocarditis is largely supportive. Strict rest, antiarrhythmic drugs (see Chapter 4), therapy to support myocardial function and manage CHF signs (see Chapter 3), and other support are used as needed. Corticosteroids are

not proven to be clinically beneficial in dogs with myocarditis, and considering the possible infective cause, they are not recommended as nonspecific therapy. Exceptions would be confirmed immune-mediated disease, drug-related or eosinophilic myocarditis, or confirmed nonresolving myocarditis.

#### **NON-INFECTIVE MYOCARDITIS**

Myocardial inflammation can result from the effects of drugs, toxins, or immunologic responses. Although there is little clinical documentation for many of these in dogs, a large number of potential causes have been identified in people. Besides the well-known toxic effects of doxorubicin and catecholamines, other potential causes of non-infective myocarditis include heavy metals (e.g., arsenic, lead, mercury), antineoplastic drugs (cyclophosphamide, 5-fluorouracil, interleukin-2, alpha-interferon), other drugs (e.g., thyroid hormone, cocaine, amphetamines, lithium), and toxins (wasp or scorpion stings, snake venom, spider bites). Immunemediated diseases and pheochromocytoma can cause myocarditis as well. Hypersensitivity reactions to many antiinfective agents and other drugs have also been identified as causes of myocarditis in people. Drug-related myocarditis is usually characterized by eosinophilic as well as lymphocytic infiltrates.

#### TRAUMATIC MYOCARDITIS

Nonpenetrating or blunt trauma to the chest and heart is more common than penetrating wounds. Cardiac arrhythmias are frequently observed after such trauma, especially in dogs. Cardiac damage can result from impact against the chest wall, compression, or acceleration-deceleration forces. Other possible mechanisms of myocardial injury and arrhythmogenesis include an autonomic imbalance, ischemia, reperfusion injury, and electrolyte and acid-base disturbances. Thoracic radiographs, serum biochemistries, circulating cardiac troponin concentrations, ECG, and echocardiography are recommended in the assessment of these cases. Echocardiography can define preexisting heart disease, global myocardial function, and unexpected cardiovascular findings, but it may not identify small areas of myocardial injury.

Arrhythmias usually appear within 24 to 48 hours after trauma, although they can be missed on intermittent ECG recordings. VPCs, ventricular tachycardia, and accelerated idioventricular rhythms (with rates of 60 to 100 beats/min or slightly faster) are more common than supraventricular tachyarrhythmias or bradyarrhythmias in these patients. Accelerated idioventricular rhythms usually are manifested only when the sinus rate slows or pauses; they are benign in most dogs with normal underlying heart function and disappear with time (generally within a week or so). Antiarrhythmic therapy for accelerated idioventricular rhythm in this setting is usually unnecessary. The patient as well as the ECG should be monitored closely. More serious arrhythmias (e.g., faster rate) or hemodynamic deterioration may require antiarrhythmic therapy (see Chapter 4).

Traumatic avulsion of AV valve papillary muscles, septal perforation, and rupture of the heart or pericardium have also been reported. Traumatic papillary muscle avulsion causes acute volume overload with acute onset of CHF. Signs of low-output failure and shock, as well as arrhythmias, can develop rapidly after cardiac trauma.

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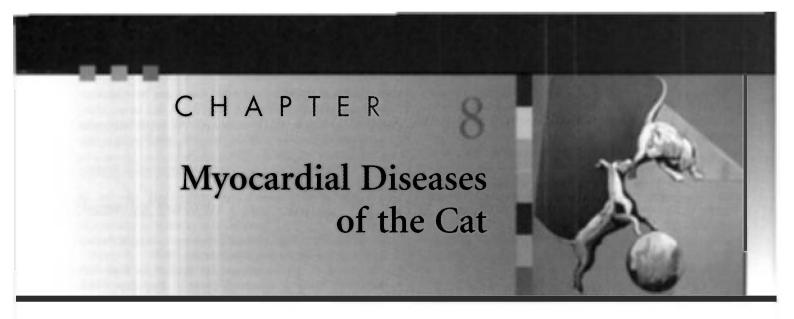
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# CHAPTER OUTLINE

# HYPERTROPHIC CARDIOMYOPATHY

Radiography

Electrocardiography

Echocardiography

Subclinical Hypertrophic Cardiomyopathy

Clinically Evident Hypertrophic Cardiomyopathy

Diuretic Therapy

Other Therapy for Acute Congestive Heart Failure

Chronic Refractory Congestive Heart Failure SECONDARY HYPERTROPHIC MYOCARDIAL

DISEASE

RESTRICTIVE CARDIOMYOPATHY

DILATED CARDIOMYOPATHY

OTHER MYOCARDIAL DISEASES

Arrhythmogenic Right Ventricular Cardiomyopathy Corticosteroid-Associated Heart Failure

Myocarditis

Myocardial disease in cats encompasses a diverse collection of idiopathic and secondary processes affecting the myocardium. The spectrum of anatomic and pathophysiologic features is wide. Disease characterized by myocardial hypertrophy is most common, although features of multiple pathophysiologic categories co-exist in some cats. Restrictive pathophysiology develops often. Classic dilated cardiomyopathy is now uncommon in cats; its features are similar to those of dilated cardiomyopathy in dogs (see Chapter 7). Myocardial disease in some cats does not fit neatly into the categories of hypertrophic, dilated, or restrictive cardiomyopathy and therefore is considered indeterminate or unclassified cardiomyopathy. Arterial thromboembolism is a major complication in cats with myocardial disease.

# HYPERTROPHIC CARDIOMYOPATHY

# **Etiology**

The cause of primary or idiopathic hypertrophic cardiomyopathy (HCM) in cats is unknown, but a heritable abnormality is likely in many cases. Disease prevalence appears to be high in several breeds, such as the Maine Coon, Persian, Ragdoll, and American Shorthair. There are also reports of HCM in litter mates and other closely related domestic shorthair cats. An autosomal dominant inheritance pattern has been found in some breeds. In human familial HCM, many different gene mutations are known to exist. Although several common human gene mutations have not yet similarly been found in feline HCM, others may be in the future. Reduced myomesin (a sarcomeric protein) occurs in some affected Maine Coon cats. The same researchers (Meurs et al. 2005) also found a mutation in cardiac myosin-binding protein C in this breed. Another mutation has been identified in Ragdoll cats; testing for these mutations is currently available (contact www.vetmed.wsu.edu/deptsVCGL/ felineTests.aspx).

In addition to mutations of genes that encode for myocardial contractile or regulatory proteins, possible causes of the disease include an increased myocardial sensitivity to or excessive production of catecholamines; an abnormal hypertrophic response to myocardial ischemia, fibrosis, or trophic factors; a primary collagen abnormality; and abnormalities of the myocardial calcium-handling process. Myocardial hypertrophy with foci of mineralization occurs in cats with hypertrophic feline muscular dystrophy, an Xlinked recessive dystrophin deficiency similar to Duchenne muscular dystrophy in people; however, congestive heart failure (CHF) is uncommon in these cats. Some cats with HCM have high serum growth hormone concentrations. It is not clear whether viral myocarditis has a role in the pathogenesis of feline cardiomyopathy. One study of myocardial samples from cats with HCM evaluated by polymerase chain reaction (PCR) showed evidence of panleukopenia virus DNA in approximately one third of the cats with myocarditis but in none of the healthy control cats (Meurs, 2000).

# **Pathophysiology**

Thickening of the left ventricular (LV) wall and/or interventricular septum is characteristic, but the extent and distribution of hypertrophy in cats with HCM are variable. Many cats have symmetric hypertrophy, but some have asymmetric septal thickening, and a few have hypertrophy limited to the free wall or papillary muscles. The LV lumen usually appears small. Focal or diffuse areas of fibrosis occur within the endocardium, conduction system, or myocardium; narrowing of small intramural coronary arteries may also be noted. Areas of myocardial infarction as well as myocardial fiber disarray may be present.

Myocardial hypertrophy and the accompanying changes increase ventricular wall stiffness. Additionally, early active myocardial relaxation may be slow and incomplete, especially in the presence of myocardial ischemia. This further reduces ventricular distensibility and promotes diastolic dysfunction. This ventricular stiffness impairs LV filling and increases diastolic pressure. LV volume remains normal or decreased. Reduced ventricular volume results in a lower stroke volume, which may contribute to neurohormonal activation. Higher heart rates further interfere with LV filling, promote myocardial ischemia, and contribute to pulmonary venous congestion and edema by shortening the diastolic filling period. Contractility, or systolic function, is usually normal in affected cats. However, some cats experience progression to ventricular systolic failure and dilation.

Progressively higher LV filling pressures lead to increased left atrial (LA) and pulmonary venous pressures. Progressive LA dilation as well as pulmonary congestion and edema can result. The degree of LA enlargement varies from mild to massive. A thrombus is sometimes found within the LV or attached to a ventricular wall, although it is more commonly located in the LA. Arterial thromboembolism is a major complication of HCM as well as other forms of cardiomy-opathy in cats (see Chapter 12). Mitral regurgitation develops in some affected cats. Changes in LV geometry, papillary muscle structure, or the systolic movement of the mitral valve (systolic anterior motion [SAM]) may prevent normal valve closure. Valve insufficiency exacerbates the increased LA size and pressure.

Systolic dynamic LV outflow obstruction occurs in some cats. This is also known as hypertrophic obstructive cardiomyopathy or functional subaortic stenosis. Excessive asymmetric hypertrophy of the basilar interventricular septum may be evident on echocardiograms or at necropsy. Systolic outflow obstruction increases LV pressure, wall stress, and myocardial oxygen demand and promotes myocardial ischemia. Mitral regurgitation is exacerbated by the tendency of hemodynamic forces to pull the anterior mitral leaflet toward the interventricular septum during ejection (SAM, see Figure 8-3). Increased LV outflow turbulence commonly causes an ejection murmur of variable intensity in these cats.

Several factors probably contribute to the development of myocardial ischemia in cats with HCM. These include narrowing of intramural coronary arteries, increased LV filling pressure, decreased coronary artery perfusion pressure, and insufficient myocardial capillary density for the degree of hypertrophy. Tachycardia contributes to ischemia by increasing myocardial O<sub>2</sub> requirements while reducing diastolic coronary perfusion time. Ischemia impairs early, active ventricular relaxation, which further increases ventricular filling pressure, and over time leads to myocardial fibrosis. Ischemia can provoke arrhythmias and possibly thoracic pain.

Atrial fibrillation (AF) and other tachyarrhythmias further impair diastolic filling and exacerbate venous congestion; the loss of the atrial "kick" and the rapid heart rate associated with AF are especially detrimental. Ventricular tachycardia or other arrhythmias may lead to syncope or sudden death.

Pulmonary venous congestion and edema result from increasing LA pressure. Increased pulmonary venous and capillary pressures are thought to cause pulmonary vasoconstriction; increased pulmonary arterial pressure and secondary right-sided CHF signs may occur. Eventually, refractory biventricular failure with profuse pleural effusion develops in some cats with HCM. The effusion is usually a modified transudate, although it can be (or become) chylous.

#### **Clinical Features**

HCM may be most common in middle-age male cats, but clinical signs can occur at any age. Cats with milder disease may be asymptomatic for years. Symptomatic cats are most often presented for respiratory signs of variable severity or acute signs of thromboembolism (see p. 195). Respiratory signs include tachypnea; panting associated with activity; dyspnea; and, only rarely, coughing (which can be misinterpreted as vomiting). Disease onset may seem acute in sedentary cats, even though pathologic changes have developed gradually. Occasionally, lethargy or anorexia is the only evidence of disease. Some cats have syncope or sudden death in the absence of other signs. Stresses such as anesthesia, surgery, fluid administration, systemic illnesses (e.g., fever or anemia), or boarding can precipitate CHF in an otherwise compensated cat. Asymptomatic disease is discovered in some cats when a murmur or gallop sound is heard during routine auscultation.

Systolic murmurs compatible with mitral regurgitation or LV outflow tract obstruction are common. Some cats do not have an audible murmur, even those with marked ventricular hypertrophy. A diastolic gallop sound (usually S<sub>4</sub>) may be heard, especially if heart failure is evident or imminent. Cardiac arrhythmias are relatively common. Femoral pulses are usually strong, unless distal aortic thromboembolism has occurred. The precordial impulse often feels vigorous. Prominent lung sounds, pulmonary crackles, and sometimes cyanosis accompany severe pulmonary edema. Pulmonary crackles are not always heard with edema in cats. Pleural effusion usually attenuates ventral pulmonary sounds. The physical examination may be normal in subclinical cases.

# Diagnosis

# **RADIOGRAPHY**

Radiographic features of HCM include a prominent left atrium and variable LV enlargement (Fig. 8-1). The classic valentine-shaped appearance of the heart on dorsoventral or ventrodorsal views is not always present, although usually the point of the left ventricular apex is maintained. The cardiac silhouette appears normal in most cats with mild HCM. Enlarged and tortuous pulmonary veins may be noted in cats with chronically high LA and pulmonary venous pressure. Left-sided CHF produces variable degrees of patchy interstitial or alveolar pulmonary edema infiltrates. The radiographic distribution of pulmonary edema is variable; a diffuse or focal distribution throughout the lung fields is common, in contrast to the characteristic perihilar distribution of cardiogenic pulmonary edema seen in dogs. Pleural effusion is common in cats with advanced or biventricular CHF.

#### **ELECTROCARDIOGRAPHY**

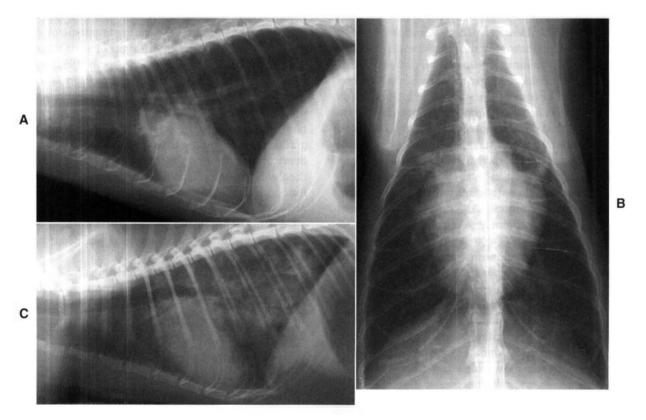
Many (up to 70%) cats with HCM have electrocardiogram (ECG) abnormalities. These include criteria for LA or LV enlargement, ventricular and/or (less often) supraventricular tachyarrhythmias, and a left anterior fascicular block pattern

(Fig. 8-2). Atrioventricular (AV) conduction delay, complete AV block, or sinus bradycardia is occasionally found.

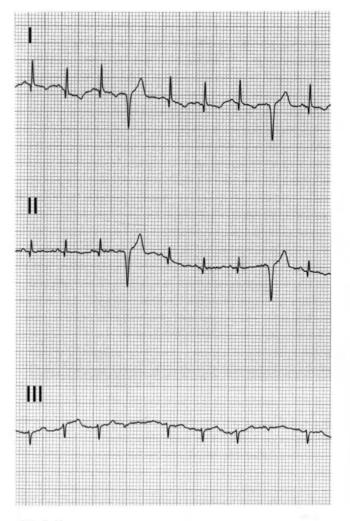
#### **ECHOCARDIOGRAPHY**

Echocardiography is the best means of diagnosis and differentiation of HCM from other disorders. The extent of hypertrophy and its distribution within the ventricular wall, septum, and papillary muscles is shown by two-dimensional and M-mode echo studies. Doppler techniques can demonstrate LV diastolic or systolic abnormalities.

Widespread myocardial thickening is common, and the hypertrophy is often asymmetrically distributed among various LV wall, septal, and papillary muscle locations. Focal areas of hypertrophy also occur. Use of two-dimensional-guided M-mode helps ensure proper beam position. Standard M-mode views and measurements are obtained, but thickened areas outside these standard positions should also be measured (Fig. 8-3). The diagnosis of early disease may be questionable in cats with mild or only focal thickening. Falsely increased thickness measurements (pseudohypertrophy) can occur with dehydration and sometimes tachycardia. Spurious diastolic thickness measurements also arise when the beam does not transect the wall/septum perpendicularly and when the measurement is not taken at the end of diastole, as can happen without simultaneous ECG record-



Radiographic examples of feline hypertrophic cardiomyopathy. Lateral (A) and dorsoventral (B) views showing atrial and mild ventricular enlargement in a male Domestic Shorthair cat. Lateral (C) view of a cat with hypertrophic cardiomyopathy and marked pulmonary edema.



# FIG 8-2 Electrocardiogram from a cat with hypertrophic cardiomyopathy showing occasional ventricular premature complexes and a left axis deviation. Leads I, II, III, at 25 mm/sec.

1 cm = 1 mV.

ing or when using two-dimensional imaging of insufficient frame rate. A (properly obtained) diastolic LV wall or septal thickness >5.5 mm is considered abnormal. Cats with severe HCM have diastolic LV wall or septal thicknesses of 8 mm or more, although the degree of hypertrophy is not necessarily correlated with the severity of clinical signs. Doppler-derived estimates of diastolic function, such as isovolumic relaxation time, and mitral inflow and pulmonary venous velocity patterns, as well as Doppler tissue imaging techniques are being employed more often to define disease characteristics.

Papillary muscle hypertrophy can be marked, and systolic LV cavity obliteration is observed in some cats. Increased echogenicity (brightness) of papillary muscles and subendocardial areas is thought to be a marker for chronic myocardial ischemia with resulting fibrosis. LV fractional shortening (FS) is generally normal to increased. However, some cats have mild to moderate LV dilation and reduced contractility (FS ~ 23%-29%; normal FS is 35%-65%). Right ventricular

enlargement and pericardial or pleural effusion are occasionally detected.

Cats with dynamic LV outflow tract obstruction also often have SAM of the mitral valve (Fig. 8-4) or premature closure of the aortic valve leaflets on M-mode scans. Doppler modalities can demonstrate mitral regurgitation and LV outflow turbulence (Fig. 8-5), although optimal alignment with the maximal-velocity outflow jet is often difficult and it is easy to underestimate the systolic gradient.

LA enlargement may be mild to marked. Spontaneous contrast (swirling, smoky echos) is visible within the enlarged LA of some cats. This is thought to result from blood stasis with cellular aggregations and to be a harbinger of thromboembolism. A thrombus is occasionally visualized within the left atrium, usually in the auricle (Fig. 8-6).

Other causes of myocardial hypertrophy (see p. 149) should be excluded before a diagnosis of idiopathic HCM is made. Myocardial thickening can also result from infiltrative disease. Variation in myocardial echogenicity or wall irregularities may be noted in such cases. Excess moderator bands appear as bright, linear echos within the left ventricular cavity.

# **Clinicopathologic Findings**

Clinical pathology tests are often noncontributory. High concentrations of circulating natriuretic peptides and cardiac troponins occur in cats with moderate to severe HCM. Variably elevated plasma TNF $_{\alpha}$  concentrations have been found in cats with CHF.

# Treatment

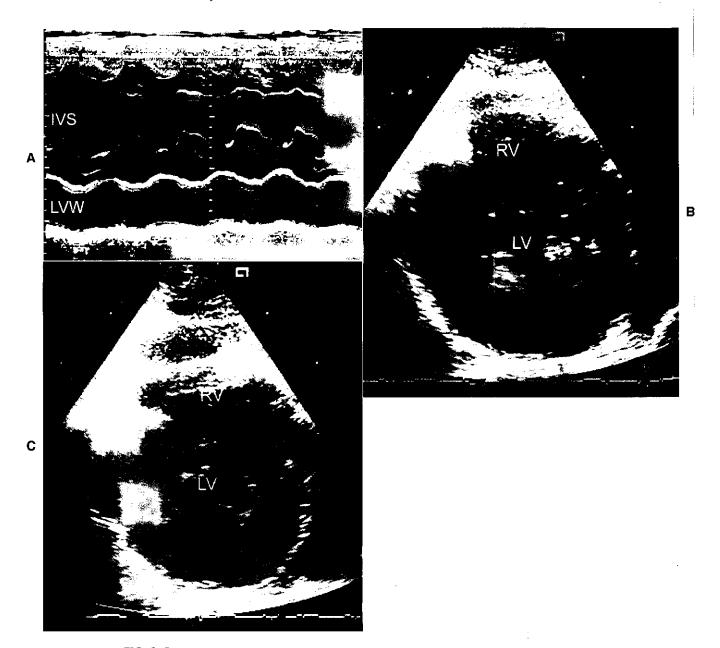
# SUBCLINICAL HYPERTROPHIC CARDIOMYOPATHY

Whether (and how) asymptomatic cats should be treated is controversial. It is unclear if disease progression can be slowed or survival prolonged by medical therapy before the onset of clinical signs. According to anecdotal reports, some cats show increased activity or improved "attitude" after being treated with a  $\beta$ -blocker or diltiazem on the basis of echocardiographic findings or an arrhythmia. When moderate to severe LA enlargement is found, especially with spontaneous echocontrast, instituting antithrombotic prophylaxis is prudent (see Chapter 12).

Avoidance of stressful situations likely to cause persistent tachycardia and reevaluation on a semiannual or annual basis are usually advised. Secondary causes of myocardial hypertrophy, such as systemic arterial hypertension and hyperthyroidism, should be ruled out (or treated, if found).

# CLINICALLY EVIDENT HYPERTROPHIC CARDIOMYOPATHY

Goals of therapy are to enhance ventricular filling, relieve congestion, control arrhythmias, minimize ischemia, and prevent thromboembolism (Box 8-1). Furosemide is used only at the dosage needed to help control congestive signs. Moderate to severe pleural effusion is treated by thoraco-

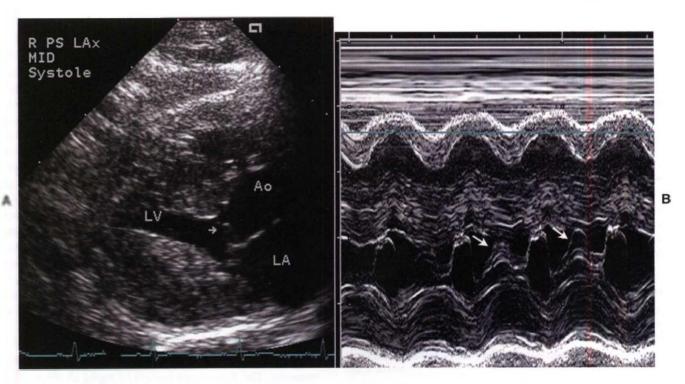


Echocardiographic examples of feline hypertrophic cardiomyopathy. M-mode image (A) at the left ventricular level from a 7-year-old male Domestic Shorthair cat. The left ventricular diastolic free-wall and septal thicknesses are about 8 mm. Two-dimensional right parasternal short-axis views during diastole (B) and systole (C) in male Maine Coon cat with hypertrophic obstructive cardiomyopathy. In (B) note the hypertrophied and bright papillary muscles. In (C) note the almost total systolic obliteration of the left ventricular chamber. IVS, interventricular septum; LV, left ventricle; LVW, left ventricular free wall; RV, right ventricle.

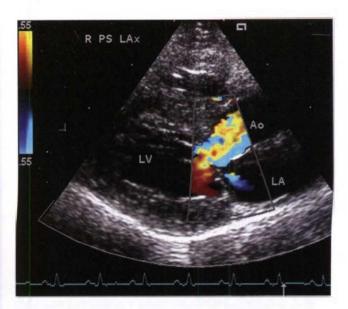
centesis, with the cat restrained gently in sternal position. Cats with severe CHF signs are given supplemental oxygen, parenteral furosemide, and sometimes other drugs to control edema (discussed in more detail later). Once initial medications have been given, the cat should be allowed to rest. The respiratory rate is noted initially and then every 30 minutes or so without disturbing the cat. Catheter placement, blood sampling, radiographs, and other tests and

therapies should be delayed until the cat's condition is more stable.

Ventricular filling is improved by slowing the heart rate and enhancing relaxation. Stress and activity level should be minimized to the extent possible. Although the Ca<sup>++</sup>-channel blocker diltiazem, or a  $\beta$ -blocker (see Chapter 4 and Table 4-2) have historically formed the foundation of long-term oral therapy, an angiotensin-converting enzyme inhibitor

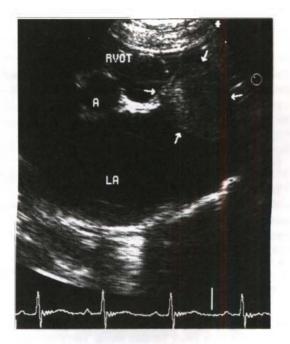


**A,** Two-dimensional echo image in midsystole from the cat in *Fig. 8-3*, *B* and *C*. Echoes from the anterior mitral leaflet appear within the LV outflow tract (arrow) because of abnormal systolic anterior (toward the septum) motion (SAM) of the valve. **B,** The M-mode echocardiogram at the mitral valve level also shows the mitral SAM (arrows). Ao, Aorta;



LA, left atrium; LV, left ventricle.

Color flow Doppler image taken in systole from a male Domestic Longhair cat with hypertrophic obstructive cardiomyopathy. Note the turbulent flow just above where the thickened interventricular septum protrudes into the left ventricular outflow tract and a small mitral insufficiency jet into the LA, common with SAM. Right parasternal long axis view. Ao, Aorta; LA, left atrium; LV, left ventricle.



Echocardiogram obtained from the right parasternal short-axis position at the aortic-left atrial level in an old male Domestic Shorthair cat with restrictive cardiomyopathy. Note the massive left atrial enlargement and thrombus (arrows) within the auricle. A, Aorta; LA, left atrium; RVOT, right ventricular outflow tract.



BOX 8-1

Treatment Outline for Cats with Hypertrophic Cardiomyopathy

#### Severe, Acute Signs of CHF\*

Supplemental O<sub>2</sub>

Minimize patient handling

Furosemide (parenteral)

Thoracocentesis, if pleural effusion present

Heart rate control and antiarrhythmic therapy, if indicated (can use IV diltiazem, esmolol, [+/-] or propranolol)†

+/- nitroglycerin (cutaneous)

+/- bronchodilator (e.g., aminophylline or theophylline)

+/- sedation

Monitor: respiratory rate, HR and rhythm, arterial blood pressure, renal function, serum electrolytes, etc.

#### Mild To Moderate Signs of CHF\*

ACE inhibitor

β-blocker (e.g., atenolol) or diltiazem

Furosemide

Antithrombotic prophylaxis (aspirin, clopidogrel, heparin, LMWH, or warfarin)‡

Exercise restriction

Reduced-salt diet, if the cat will eat it

#### Chronic HCM Management\*

ACE inhibitor

β-blocker (e.g., atenolol) or diltiazem

Furosemide (lowest effective dosage and frequency)

Antithrombotic prophylaxis (aspirin, clopidogrel, heparin, LMWH, or warfarin)‡

Thoracocentesis as needed

+/- Spironolactone and/or hydrochlorothiazide

+/- Concurrent β-blocker and diltiazem therapy

+/- Additional antiarrhythmic drug therapy, if indicated Home monitoring of resting respiratory rate (+HR if possible)

Dietary salt restriction, if accepted

Monitor renal function, electrolytes, etc.

Manage other medical problems (rule out hyperthyroidism and hypertension if not done previously)

+/- Positive inotropic drug (only for deteriorating systolic function without LV outflow obstruction)

ACE, Angiotensin-converting enzyme; CHF, congestive heart failure; HR, heart rate; LMWH, low-molecular-weight heparin.

(ACEI) may have greater benefit in cats with CHF. Optimal recommendations await further study. The decision to use one particular drug over another is influenced by echocardiographic or other findings in the individual cat or the response to medication. Diltiazem is often used when severe, symmetric LV hypertrophy is present. A β-blocker is currently preferred for cats with dynamic LV outflow obstruction, tachyarrhythmias, syncope, suspected myocardial

infarction, or concurrent hyperthyroidism. An ACEI may reduce neurohormonal activation and abnormal cardiac remodeling. It is sometimes used alone or combined with diltiazem or a  $\beta$ -blocker. Long-term therapy generally also includes therapy to reduce the likelihood of arterial thromboembolism (see Chapter 12). Dietary sodium restriction is recommended if the cat will accept such a diet, but it is more important to forestall anorexia.

Certain drugs are generally discouraged in cats with HCM. These include digoxin and other positive inotropic agents because they increase the myocardial oxygen demand and can worsen dynamic LV outflow obstruction. Any drug that accelerates the heart rate is also potentially detrimental because tachycardia shortens ventricular filling time and predisposes to myocardial ischemia. Arterial vasodilators can cause hypotension and reflex tachycardia, and cats with HCM have little preload reserve. Hypotension can also exacerbate dynamic outflow obstruction. Although ACEIs have this potential, their vasodilating effects are usually mild.

# **Diuretic Therapy**

Cats with severe pulmonary edema are usually given intramuscular (IM) furosemide initially (2 mg/kg q1-4h; see Box 3-1 and p. 58), until an IV catheter can be placed without excessive stress to the cat. The respiratory rate and effort are used to guide ongoing diuretic therapy. As respiratory distress resolves, furosemide can be continued at a reduced dose (~1 mg/kg q8-12h). Once pulmonary edema is controlled, furosemide is given orally and the dose gradually titrated downward to the lowest effective level. A starting dose of 6.25 mg/cat q8-12h can be slowly reduced over days to weeks, depending on the cat's response. Some cats do well with dosing a few times per week (or less), whereas others require it several times per day. Complications of excessive diuresis include azotemia, anorexia, electrolyte disturbances, and poor LV filling. If the cat is unable to rehydrate itself by oral water intake, cautious parenteral fluid administration may be needed (e.g., 15-20 ml/kg/day of 0.45% saline, 5% dextrose in water, or other low-sodium fluid).

# Other Therapy for Acute Congestive Heart Failure

Nitroglycerin ointment may be used (q4-6h, see Box 3-1), although no studies of its efficacy in this situation have been done. The bronchodilating and mild diuretic effects of aminophylline (5 mg/kg q12h, IM, IV) may be helpful in cats with severe pulmonary edema, as long as the drug does not increase the heart rate.

Butorphanol may be used to reduce anxiety (see Box 3-1). Acepromazine may be used as an alternative and can promote peripheral redistribution of blood by its  $\beta$ -blocking effects. Hypothermia may be exacerbated by peripheral vasodilation. Morphine should not be used in cats. Airway suctioning and mechanical ventilation with positive end-expiratory pressure can be considered in extreme cases.

Angiotensin-converting enzyme inhibitors. An ACEI appears to have beneficial effects, especially in cats with

<sup>\*</sup>See text and Chapters 3 and 4 for further details.

<sup>†</sup> See Chapter 4 for additional ventricular antiarrhythmic drug therapy.

<sup>‡</sup>See Chapter 12 for further details.

refractory heart failure. Renin-angiotensin system inhibition may mitigate angiotensin II—mediated ventricular hypertrophy. ACE inhibition might reduce LA size and ventricular/septal wall thickness, at least in some cats. Enalapril and benazepril are the agents used most often in cats, although others are available (see Chapter 3 and Table 3-3).

Ca<sup>+-</sup>-channel blockers. Ca<sup>+-</sup>-channel blockers are thought to have beneficial effects in cats with HCM by modestly reducing heart rate and contractility (which reduces myocardial O₂ demand). Diltiazem promotes coronary vasodilation and may have a positive effect on myocardial relaxation. Verapamil is not recommended because of its variable bioavailability and risk of toxicity in cats. Amlodipine has primarily vasodilatory effects and is not used for HCM because it can provoke reflex tachycardia and worsen a systolic outflow gradient.

Diltiazem is well-tolerated in many cases. Longer-acting diltiazem products are more convenient for chronic use, although the serum concentrations achieved can be variable. Dilacor (diltiazem) XR, dosed at half of an internal (60-mg) tablet from the 240-mg capsule size q24(-12)h, or Cardizem CD, compounded and dosed at 10 mg/kg q24h, are most often used.

**β-adrenergic blockers.** β-blockers can reduce heart rate and dynamic LV outflow obstruction to a greater extent than diltiazem. They are also used to suppress tachyarrhythmias in cats. Sympathetic inhibition also leads to reduced myocardial  $O_2$  demand, which can be important in cats with myocardial ischemia or infarction. By inhibiting catecholamine-induced myocyte damage, β-blockers may reduce myocardial fibrosis. β-blockers can slow active myocardial relaxation, although the benefits of heart rate reduction may outweigh this.

Atenolol (see Chapter 4) is used most commonly. Propranolol or another nonselective  $\beta$ -blocker can also be used, but these should be avoided until pulmonary edema is largely resolved. Antagonism of airway  $\beta_2$ -receptors leading to bronchoconstriction is a concern when using nonselective agents in CHF. Propranolol (a lipid soluble drug) causes lethargy and depressed appetite in some cats.

Occasionally, a  $\beta$ -blocker is added to diltiazem therapy (or vice versa) in cats with chronic refractory failure or to further reduce heart rate in cats with AF. However, care must be taken to prevent bradycardia or hypotension in animals receiving this combination.

# CHRONIC REFRACTORY CONGESTIVE HEART FAILURE

Refractory pulmonary edema or pleural effusion is difficult to manage. Moderate to large pleural effusions should be treated by thoracocentesis. Various medical strategies may help slow the rate of abnormal fluid accumulation, including maximizing the dosage of (or adding) an ACEI; increasing the dosage of furosemide (up to 4 mg/kg q8h); increasing the dose of diltiazem or  $\beta$ -blocker for greater heart rate control; and adding spironolactone, with or without hydrochlorothiazide (see Table 3-3). Spironolactone can be compounded

into a flavored suspension for more accurate dosing. Pimobendan or digoxin can also be used for treating refractory right-sided CHF signs in cats without LV outflow obstruction and those with progressive LV dilation and myocardial systolic failure in end-stage disease. Frequent monitoring for the development of azotemia or electrolyte disturbances is warranted.

# **Prognosis**

Several factors influence the prognosis for cats with HCM, including the speed with which the disease progresses, the occurrence of thromboembolic events and/or arrhythmias, and the response to therapy. Asymptomatic cats with only mild to moderate LV hypertrophy and atrial enlargement often live well for several years. Cats with marked LA enlargement and more severe hypertrophy appear to be at greater risk for CHF, thromboembolism, and sudden death. LA size and age (i.e., older cats) appear to be negatively correlated with survival. Median survival time for cats with CHF is probably between 1 to 2 years. The prognosis is worse in cats with AF or refractory right-sided CHF. Thromboembolism and CHF confer a guarded prognosis (median survival of 2 to 6 months), although some cats do well if congestive signs can be controlled and infarction of vital organs has not occurred. Recurrence of thromboembolism is common.

# SECONDARY HYPERTROPHIC MYOCARDIAL DISEASE

Myocardial hypertrophy is a compensatory response to certain identifiable stresses or diseases. Marked LV wall and septal thickening and clinical heart failure can occur in some of these cases, although they are generally not considered to be idiopathic HCM. Secondary causes should be ruled out whenever LV hypertrophy is identified.

Evaluation for hyperthyroidism is indicated in cats 6 years of age or older with myocardial hypertrophy. Hyperthyroidism alters cardiovascular function by its direct effects on the myocardium and through the interaction of heightened sympathetic nervous system activity and excess thyroid hormone on the heart and peripheral circulation. Cardiac effects of thyroid hormone include myocardial hypertrophy and increased heart rate and contractility. The metabolic acceleration that accompanies hyperthyroidism causes a hyperdynamic circulatory state characterized by increased cardiac output, oxygen demand, blood volume, and heart rate. Systemic hypertension can further stimulate myocardial hypertrophy. Manifestations of hyperthyroid heart disease often include a systolic murmur, hyperdynamic arterial pulses, a strong precordial impulse, sinus tachycardia, and various arrhythmias. Criteria for IV enlargement or hypertrophy are often found on ECG, thoracic radiographs, or echocardiogram. Signs of CHF develop in approximately 15% of hyperthyroid cats; most have normal to high FS, but a few have poor contractile function. Cardiac therapy, in addition to treatment of the hyperthyroidism, may be necessary for these cats. A  $\beta$ -blocker can temporarily control many of the adverse cardiac effects of excess thyroid hormone, especially tachyarrhythmias. Diltiazem is an alternative therapy. Treatment for CHF is the same as that described for HCM. The rare hypodynamic (dilated) cardiac failure is treated in the same way as dilated cardiomyopathy. Cardiac therapy, including a  $\beta$ -blocker, is not a substitute for antithyroid treatment.

IV concentric hypertrophy is the expected response to increased ventricular systolic pressure (afterload). Systemic arterial hypertension (see Chapter 11) increases afterload because of high arterial pressure and resistance. Increased resistance to ventricular outflow also occurs with a fixed (e.g., congenital) subaortic stenosis or dynamic LV outflow tract obstruction (hypertrophic obstructive cardiomyopathy). Cardiac hypertrophy also develops in cats with hypersomatotropism (acromegaly) as a result of growth hormone's trophic effects on the heart. CHF occurs in some of these cats. Increased myocardial thickness occasionally results from infiltrative myocardial disease, most notably from lymphoma.

# RESTRICTIVE CARDIOMYOPATHY

# **Etiology and Pathophysiology**

Restrictive cardiomyopathy (RCM) is associated with extensive endocardial, subendocardial, or myocardial fibrosis. The cause is not clear but probably is multifactorial. This condition may be a consequence of endomyocarditis or the endstage of myocardial failure and infarction caused by HCM. Neoplastic (e.g., lymphoma) or other infiltrative or infectious diseases occasionally causes a secondary RCM.

There are a variety of histologic findings in cats with RCM, including marked perivascular and interstitial fibrosis, intramural coronary artery narrowing, and myocyte hypertrophy, as well as areas of degeneration and necrosis. Some cats have extensive LV endomyocardial fibrosis with chamber deformity, or fibrous tissue bridging between the septum and LV wall. The mitral apparatus and papillary muscles may be fused to surrounding tissue or distorted.

LA enlargement is prominent in cats with RCM, as a consequence of chronically high LV filling pressure from increased LV wall stiffness. The LV may be normal to reduced in size or mildly dilated. LV hypertrophy is variably present and may be regional. Intracardiac thrombi and systemic thromboembolism are common.

LV fibrosis impairs diastolic filling. Most affected cats have normal to only mildly reduced contractility, but this may progress with time as more functional myocardium is lost. Some cases develop regional LV dysfunction, possibly from myocardial infarction, which decreases overall systolic function. These cases are perhaps better considered unclassified rather than restrictive. If mitral regurgitation is present, it is usually mild. Arrhythmias, ventricular dilation, and myocardial ischemia or infarction also contribute to the development of diastolic dysfunction. Chronically elevated

left heart filling pressures, combined with compensatory neurohormonal activation, leads to left-sided or biventricular CHF. The duration of subclinical disease progression in RCM is unknown.

## **Clinical Features**

Middle-aged and older cats are most often diagnosed with RCM. Young cats are sometimes affected. Inactivity, poor appetite, vomiting, and weight loss of recent onset are common in the history. The clinical presentation varies but usually includes respiratory signs from pulmonary edema or pleural effusion. Clinical signs are often precipitated or acutely worsened by stress or concurrent disease that causes increased cardiovascular demand. Thromboembolic events are also common. Sometimes the condition is discovered by detecting abnormal heart sounds or arrhythmias on routine exam or radiographic evidence of cardiomegaly.

A systolic murmur of mitral or tricuspid regurgitation, a gallop sound, and arrhythmias are common physical examination findings. Pulmonary sounds can be abnormal in cats with pulmonary edema or pleural effusion. Femoral arterial pulses are normal or slightly weak. Jugular vein distention and pulsation are common in cats with right-sided CHF signs. Acute signs of distal aortic (or other) thromboembolism may be the reason for presentation.

# Diagnosis

Diagnostic test results are frequently similar to those in cats with HCM. Radiographs indicate LA or biatrial enlargement (sometimes massive) and LV or generalized heart enlargement (Fig. 8-7). Mild to moderate pericardial effusion contributes to the cardiomegaly in some cats. Proximal pulmonary veins may appear dilated and tortuous. Other possible radiographic findings in cats with CHF signs include infiltrates of pulmonary edema, pleural effusion, and sometimes hepatomegaly.

Common ECG abnormalities include wide QRS complexes, tall R waves, evidence of intraventricular conduction disturbances, wide P waves, and atrial tachyarrhythmias or fibrillation. Echocardiography typically shows marked LA (and sometimes right atrial [RA]) enlargement. There is variable LV wall and interventricular septal thickening. Ventricular wall motion is often normal but may be somewhat depressed (FS usually >25%). Hyperechoic areas of fibrosis within the LV wall and/or endocardial areas may be evident. Extraneous intraluminal echos representing excess moderator bands are occasionally seen. Sometimes, extensive LV endocardial fibrosis, with scar tissue bridging between the free-wall and septum, constricts part of the ventricular chamber. Right ventricular (RV) dilation is often seen. Sometimes an intracardiac thrombus is found, usually in the left auricle or left atrium, but occasionally in the left ventricle (see Fig. 8-6). Mild mitral or tricuspid regurgitation and a restrictive mitral inflow pattern can be seen with Doppler studies. Some cats have marked regional wall dysfunction, especially of the left ventricular free wall, which depresses FS, along with mild left ventricular dilation. These

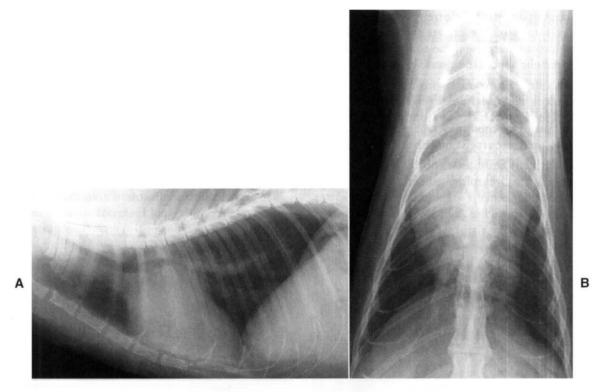


FIG 8-7
Lateral (A) and dorsoventral (B) radiographs from an older Domestic Shorthair cat with restrictive cardiomyopathy show marked left atrial enlargement and prominent proximal pulmonary veins.

may represent cases of myocardial infarction or unclassified cardiomyopathy rather than RCM.

The clinicopathologic findings are nonspecific. Pleural effusions are usually classified as modified transudate or chyle. Plasma taurine concentration is low in some affected cats and should be measured if decreased contractility is identified.

# **Treatment and Prognosis**

Therapy for acute CHF is the same as for cats with HCM (see p. 148). Cats that require inotropic support can be given dobutamine by constant rate infusion (CRI). Management of thromboembolism is described on p. 197.

Long-term therapy for heart failure includes furosemide at the lowest effective dosage; the resting respiratory rate, activity level, and radiographic findings are used to monitor efficacy. An ACEI is also used, starting with a very low dose and increasing to the usual maintenance dose (see Table 3-3). Ideally, blood pressure should be monitored when initiating or adjusting this therapy. A  $\beta$ -blocker is usually used for tachyarrhythmias or if myocardial infarction is suspected. Alternatively, diltiazem can also be used, although its value in the face of significant fibrosis is controversial. Cats that need chronic inotropic support can be given digoxin or pimobendan (see Table 3-3). Taurine supplementation may be helpful. Prophylaxis against thromboembolism is recommended (see p. 199), and a low-sodium diet should be fed, if accepted. Creatinine or the blood urea nitrogen and elec-

trolyte concentrations should be measured periodically. Furosemide and/or enalapril doses should be reduced if hypotension or azotemia occurs.

Cats with refractory heart failure and pleural effusion are difficult to manage. In addition to thoracocentesis as needed, the ACEI and furosemide dosages can be increased cautiously. Adding digoxin or pimobendan, if not already being used, may be helpful for cats with refractory failure. Other strategies include adding spironolactone (with or without hydrochlorothiazide) or nitroglycerin ointment to the regimen.

The prognosis is generally guarded to poor for cats with RCM and heart failure. Nevertheless, some cats survive more than a year after diagnosis. Thromboembolism and refractory pleural effusion commonly occur.

# **DILATED CARDIOMYOPATHY**

# Etiology

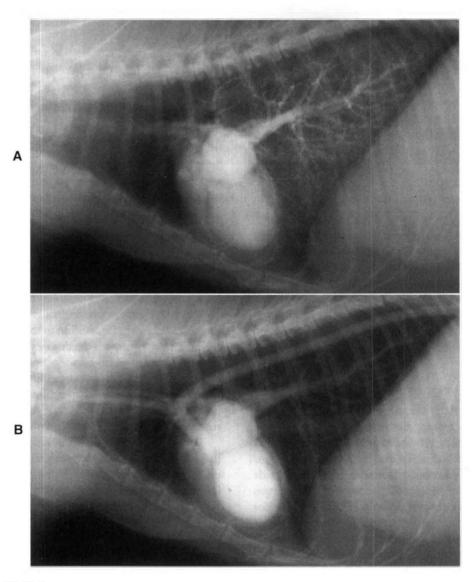
In the late 1980s taurine deficiency was identified as a major cause of dilated cardiomyopathy (DCM) in cats. This discovery prompted pet food manufacturers to increase the taurine content of commercial cat diets. Clinical DCM then became an uncommon disease in cats. Not all cats fed a taurine-deficient diet develop DCM. Other factors besides a simple deficiency of this essential amino acid are likely to be involved in the pathogenesis, including genetic factors and a possible

link with potassium depletion. Relatively few cases of DCM are identified now; many of these cats are not taurine deficient. DCM in these cats may represent the end-stage of another myocardial metabolic abnormality, toxicity, or infection.

Doxorubicin causes characteristic myocardial histologic lesions in cats as it does in dogs. Cats appear less likely to develop clinical CHF from myocardial failure. Although in very rare cases cats have echocardiographic changes consistent with DCM after receiving cumulative doses of 170 to 240 mg/m², clinically relevant doxorubicin-induced cardiomyopathy does not occur in the cat.

# **Pathophysiology**

DCM in cats has a similar pathophysiology to that in dogs (see p. 129). Poor myocardial contractility is the characteristic feature (Fig. 8-8). Usually, all cardiac chambers become dilated. AV valve insufficiency occurs secondary to chamber enlargement and papillary muscle atrophy. As cardiac output decreases, compensatory neurohormonal mechanisms are activated, leading eventually to signs of CHF and low cardiac output. Besides pulmonary edema, pleural effusion and arrhythmias are common in cats with DCM.



Nonselective angiogram from a 13-year-old female Siamese cat with dilated cardiomyopathy. A bolus of radiographic contrast material was injected into the jugular vein. **A,** Three seconds after injection, some contrast medium remains in the right ventricle and pulmonary vasculature. Dilated pulmonary veins are seen entering the left atrium. Note the dilated left atrium and ventricle. **B,** Thirteen seconds after the injection, the left heart and pulmonary veins are still opacified, illustrating the poor cardiac contractility and extremely slow circulation time. The thin left ventricular caudal wall and papillary muscles are better seen in this frame.

# **Clinical Features**

DCM can occur at any age, although most affected cats are late-middle aged to geriatric. There is no breed or gender predilection. Clinical signs often include anorexia, lethargy, increased respiratory effort or dyspnea, dehydration, and hypothermia. Subtle evidence of poor ventricular function is usually found in conjunction with signs of respiratory compromise. Jugular venous distention, an attenuated precordial impulse, weak femoral pulses, a gallop sound (usually S<sub>3</sub>), and a left or right apical systolic murmur (of mitral or tricuspid regurgitation) are common. Bradycardia and arrhythmias are frequently heard, although many cats have a normal sinus rhythm. Increased lung sounds and pulmonary crackles can be auscultated in some cats, but pleural effusion may muffle ventral lung sounds. Some cats have signs of arterial thromboembolism (see p. 195).

# Diagnosis

Generalized cardiomegaly with rounding of the cardiac apex is often seen on radiographs. Pleural effusion is common and may obscure the heart shadow and co-existing evidence of pulmonary edema or venous congestion. Hepatomegaly may be detected; ascites is occasionally found.

Typical ECG findings include a LV enlargement pattern, AV conduction disturbance, and tachyarrhythmias. Echocardiography is an important tool to differentiate DCM from other myocardial pathophysiology. Findings are analogous to those in dogs with DCM (see p. 131). Some cats have areas of focal hypertrophy with hypokinesis of only the LV wall or septum. These may represent indeterminant myocardial disease rather than typical DCM. An intracardiac thrombus is identified in some cats, more often within the left atrium.

Nonselective angiocardiography is a more risky alternative to echocardiography, as with other cardiomyopathies. Characteristic angiographic findings include generalized chamber enlargement, atrophied papillary muscles, small aortic diameter, and slow circulation time (see Fig. 8-8). Complications of angiography, especially in cats with poor myocardial function or CHF, include vomiting and aspiration, arrhythmias, and cardiac arrest. The pleural effusion in cats with DCM is usually a modified transudate, although it can be chylous. Prerenal azotemia, mildly increased liver enzyme activity, and a stress leukogram are common clinicopathologic findings. Cats with arterial thromboembolism often have high serum muscle enzyme activities and may have an abnormal hemostasis profile. Plasma or whole blood taurine concentration measurement is recommended. Specific instructions for sample collection and mailing should be obtained from the specific laboratory. Plasma taurine concentrations are influenced by the amount of taurine in the diet, the type of diet, and the time of sampling in relation to eating; however, a plasma taurine concentration of 20 to 30 nmol/ml or less in a cat with DCM is diagnostic for taurine deficiency. Non-anorexic cats with a plasma taurine concentration of <60 nmol/ml probably should receive taurine supplementation or a different diet. Whole blood samples produce more consistent results than plasma

samples. Normal whole blood taurine concentrations exceed 200 nmol/ml; <140 nmol/ml is considered deficient.

# **Treatment and Prognosis**

The goals of treatment are analogous to those for dogs with DCM. Pleural fluid is removed by thoracocentesis. In cats with acute CHF, furosemide is given to promote diuresis, as described for HCM. Overly aggressive diuresis is discouraged because it can markedly reduce cardiac output in these cases with poor systolic function. Supplemental O2 is recommended. The venodilator nitroglycerin may be helpful in cats with severe pulmonary edema. ACEI therapy is begun as soon as oral medication can be safely given. Other vasodilators (nitroprusside, hydralazine, or amlodipine) may help maximize cardiac output, although they increase the risk of hypotension (see Box 3-1). Blood pressure, hydration, renal function, electrolyte balance, and peripheral perfusion should be monitored closely. Hypothermia is common in cats with decompensated DCM; external warming is provided as needed.

Positive inotropic support is indicated. Dobutamine (or dopamine) is administered by CRI for critical cases (see p. 60 and Box 3-1). Possible adverse effects include seizures or tachycardia; if they occur, the infusion rate is decreased by 50% or discontinued. Oral inotropic therapy with pimobendan or digoxin (see p. 65 and Table 3-3) for maintenance therapy may be instituted. Digoxin tablets are usually used because the elixir is distasteful to many cats. Toxicity can easily occur, especially in cats receiving concurrent drug therapy; serum digoxin concentration should be monitored if this drug is used (see p. 66).

Sometimes the diuretic and vasodilator therapy used for acute CHF leads to hypotension and can predispose to cardiogenic shock in cats with DCM. Half-strength saline solution with 2.5% dextrose or other low-sodium fluids can be used intravenously with caution to help support blood pressure (e.g., 20 to 35 ml/kg/day in several divided doses or by CRI); potassium supplementation may be needed. Fluid can be administered subcutaneously if necessary, although its absorption from the extravascular space may be impaired in these cases.

Chronic therapy for DCM in cats that survive acute CHF includes oral furosemide (tapered to the lowest effective dosage), an ACEI, pimobendan or digoxin, antithrombotic prophylaxis (p. 199), and (if the patient is taurine deficient) supplemental taurine or a high-taurine diet. Taurine supplementation is instituted as soon as practical, at 250 to 500 mg orally q12h, when plasma taurine concentration is low or cannot be measured. Clinical improvement, if it occurs, is generally not apparent until after the first 1 to 2 weeks of taurine supplementation, so supportive cardiac care is vital.

Improved systolic function is seen echocardiographically within 6 weeks of starting taurine supplementation in most taurine-deficient cats. Drug therapy may become unnecessary in some cats after 6 to 12 weeks, but resolution of pleural effusion and pulmonary edema should be confirmed before weaning the cat from medications. If normal systolic func-

tion, based on echocardiography, returns, the patient can be slowly weaned from supplemental taurine as long as a diet known to support adequate plasma taurine concentrations (e.g., most name-brand commercial foods) is consumed. Dry diets with 1000 to 1200 mg of taurine per kilogram of dry weight and canned diets with 2000 to 2500 mg of taurine per kilogram of dry weight are thought to maintain normal plasma taurine concentrations in adult cats. Reevaluation of the plasma taurine concentration 2 to 4 weeks after discontinuing the supplement is advised.

Taurine-deficient cats that survive a month after initial diagnosis often can be weaned from all or most medications and appear to have approximately a 50% chance for 1-year survival. The prognosis for cats that do not receive taurine supplements or do not respond to taurine is guarded to poor. Thromboembolism in cats with DCM is a grave sign.

#### OTHER MYOCARDIAL DISEASES

# ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an idiopathic cardiomyopathy that is similar to the uncommon ARVC in people. Characteristic features include moderate to severe RV chamber dilation, with either focal or diffuse RV wall thinning. RV wall aneurysm is also common. Dilation of the right atrium and, less commonly, the left atrium may occur. Myocardial atrophy with fatty and/or fibrous replacement tissue, focal myocarditis, and evidence of apoptosis are typical histologic findings. These are most prominent in the RV wall. Fibrous tissue or fatty infiltration is sometimes found in the LV and atrial walls.

Signs of right-sided CHF are common, with labored respirations caused by pleural effusion, jugular venous distention, ascites or hepatosplenomegaly, and occasionally syncope. Lethargy and inappetence without overt heart failure are sometimes the presenting signs.

Thoracic radiographs indicate right heart and sometimes LA enlargement. Pleural effusion is common. Ascites, caudal vena caval distention, and evidence of pericardial effusion may also occur. The ECG can document various arrhythmias in affected cats, including ventricular premature complexes (VPCs), ventricular tachycardia, AF, and supraventricular tachyarrhythmias. A right bundle branch block pattern appears to be common; some cats have first-degree AV block. Echocardiography shows severe RA and RV enlargement. Other possible findings include abnormal muscular trabeculation, aneurysmal dilation, areas of dyskinesis, and paradoxical septal motion. Tricuspid regurgitation appears to be a consistent finding on Doppler exam.

The prognosis is guarded once signs of heart failure appear. Recommended therapy includes diuretics as necessary, an ACEI, and digoxin (or pimobendan). Additional antiarrhythmic therapy may be needed (see Chapter 4). In people with ARVC, various tachyarrhythmias are a prominent feature and sudden death is common.

# CORTICOSTEROID-ASSOCIATED HEART FAILURE

Some cats develop CHF after receiving corticosteroid therapy. It is unclear whether this represents a previously unrecognized form of feline heart failure, unrelated to preexisting HCM, hypertension, or hyperthyroidism. An acute onset of lethargy, anorexia, tachypnea, and respiratory distress is described in affected cats. Most cats have normal auscultatory findings without tachycardia.

Moderate cardiomegaly, with diffuse pulmonary infiltrates and mild or moderate pleural effusion, appears to be typical on radiographic examination. Possible ECG findings include sinus bradycardia, intraventricular conduction abnormalities, atrial standstill, atrial fibrillation, and VPCs. On echocardiogram, most affected cats have some degree of LV wall or septal hypertrophy and LA enlargement. Some have AV valve insufficiency or abnormal systolic mitral motion.

CHF is treated in the same way as HCM; corticosteroids should be discontinued. Partial resolution of abnormal cardiac findings and successful weaning from cardiac medications are reported in some cats.

#### **MYOCARDITIS**

Inflammation of the myocardium and adjacent structures may occur in cats, as it does in other species (see also p. 137). In one study myocarditis was histologically identified in samples from more than half of cardiomyopathic cats but none from cats in the control group; viral DNA (panleukopenia) was found in about one third of the cats with myocarditis. However, the possible role of viral myocarditis in the pathogenesis of cardiomyopathy is not clear. Severe, widespread myocarditis may cause CHF or fatal arrhythmias. Cats with focal myocardial inflammation may be asymptomatic. Acute and chronic viral myocarditis have been suspected. A viral cause is rarely documented, although feline coronavirus has been identified as a cause of pericarditis-epicarditis.

Endomyocarditis has been documented mostly in young cats. Acute death, with or without preceding signs of pulmonary edema for 1 to 2 days, is the most common presentation. Histopathologic characteristics of acute endomyocarditis include focal or diffuse lymphocytic, plasmacytic, and histiocytic infiltrates with few neutrophils. Myocardial degeneration and lysis are seen adjacent to the infiltrates. Chronic endomyocarditis may have a minimal inflammatory response but much myocardial degeneration and fibrosis. RCM could represent the end stage of nonfatal endomyocarditis. Therapy involves managing CHF signs and arrhythmias, and other supportive care.

Bacterial myocarditis may develop in association with sepsis or as a result of bacterial endocarditis or pericarditis. Experimental *Bartonella* sp. infection can cause subclinical lymphoplasmacytic myocarditis, but it is unclear whether natural infection plays a role in the development of cardiomyopathy in cats. *Toxoplasma gondii* occasionally has been associated with myocarditis, usually in immunosuppressed

cats as part of a generalized disease process. Traumatic myocarditis is recognized infrequently in cats.

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# C H A P T E R Pericardial Disease and Cardiac Tumors

#### **CHAPTER OUTLINE**

GENERAL CONSIDERATIONS
CONGENITAL PERICARDIAL DISORDERS

Peritoneopericardial Diaphragmatic Hernia Other Pericardial Anomalies

PERICARDIAL EFFUSION

Hemorrhage

Transudates

Exudates

Cardiac Tamponade

Radiography

Electrocardiography

Echocardiography

Clinicopathologic Findings

Pericardiocentesis

CONSTRICTIVE PERICARDIAL DISEASE

CARDIAC TUMORS

#### GENERAL CONSIDERATIONS

Several diseases of the pericardium and intrapericardial space can disrupt cardiac function. Normally, the pericardium anchors the heart in place and provides a barrier to infection or inflammation from adjacent tissues. The pericardium is a closed serosal sac that envelops the heart and is attached to the great vessels at the heartbase. Directly adhered to the heart is the visceral pericardium, or epicardium, which is composed of a thin layer of mesothelial cells. This layer reflects back over itself at the base of the heart to line the outer fibrous parietal layer. A small amount (~0.25 ml/kg body weight) of clear, serous fluid normally serves as a lubricant between these layers. The pericardium helps balance the output of the right and left ventricles and limits acute distention of the heart, although there are few overt clinical consequences associated with its removal.

Excess or abnormal fluid accumulation in the pericardial sac is the most common pericardial disorder, and it occurs

most often in dogs. Other acquired and congenital pericardial diseases are seen infrequently. Acquired pericardial disease causing clinical signs is uncommon in cats.

#### CONGENITAL PERICARDIAL DISORDERS

#### PERITONEOPERICARDIAL DIAPHRAGMATIC HERNIA

Peritoneopericardial diaphragmatic hernia (PPDH) is the most common pericardial malformation in dogs and cats. It occurs when abnormal embryonic development (probably of the septum transversum) allows persistent communication between the pericardial and peritoneal cavities at the ventral midline. The pleural space is not involved. Other congenital defects, such as umbilical hernia, sternal malformations, and cardiac anomalies may co-exist with PPDH. Abdominal contents herniate into the pericardial space to a variable degree and cause associated clinical signs. Although the peritoneal-pericardial communication is not trauma induced, trauma can facilitate movement of abdominal contents through a preexisting defect.

#### **Clinical Features**

The initial onset of clinical signs associated with PPDH can occur at any age (ages between 4 weeks and 15 years have been reported). The majority of cases are diagnosed during the first 4 years of life, usually within the first year. In some animals clinical signs never develop. Males appear to be affected more frequently than females, and Weimaraners may be predisposed. The malformation is common in cats as well.

Clinical signs usually relate to the gastrointestinal (GI) or respiratory system. Vomiting, diarrhea, anorexia, weight loss, abdominal pain, cough, dyspnea, and wheezing are most often reported; shock and collapse may also occur. Possible physical examination findings include muffled heart sounds on one or both sides of the chest; displacement or attenuation of the apical precordial impulse; an "empty" feel on abdominal palpation (with herniation of many organs); and, rarely, signs of cardiac tamponade (discussed in more detail later).

#### Diagnosis

Thoracic radiographs are often diagnostic or highly suggestive of PPDH. Enlargement of the cardiac silhouette, dorsal tracheal displacement, overlap of the diaphragmatic and caudal heart borders, and abnormal fat and/or gas densities within the cardiac silhouette are characteristic findings (Fig. 9-1, A and B). A pleural fold, extending between the caudal heart shadow and the diaphragm ventral to the caudal vena cava on lateral view, is usually evident. Gas-filled loops of bowel crossing the diaphragm into the pericardial sac, a small liver, and few organs within the abdominal cavity may also be seen. Echocardiography helps confirm the diagnosis when radiographic findings are equivocal (Fig. 9-2). A GI barium series is diagnostic if the stomach and/or intestines are in the pericardial cavity (Fig. 9-1, C). Fluoroscopy, nonselective angiography (especially if only falciform fat or liver has herniated), celiography, or pneumopericardiography also can aid in diagnosis. ECG changes are inconsistent; decreased amplitude complexes and axis deviations caused by cardiac position changes sometimes occur.

#### **Treatment**

Therapy involves surgical closure of the peritoneal-pericardial defect after viable organs are returned to their normal location. The presence of other congenital abnormalities and the animal's clinical signs influence the decision to operate. The prognosis in uncomplicated cases is excellent. Older animals without clinical signs may do well without surgery, especially because organs chronically adhered to the heart or pericardium may be traumatized during attempted repositioning.

#### **OTHER PERICARDIAL ANOMALIES**

Pericardial cysts are rare anomalies. They may originate from abnormal fetal mesenchymal tissue or from incarcerated omental or falciform fat associated with a small PPDH. The

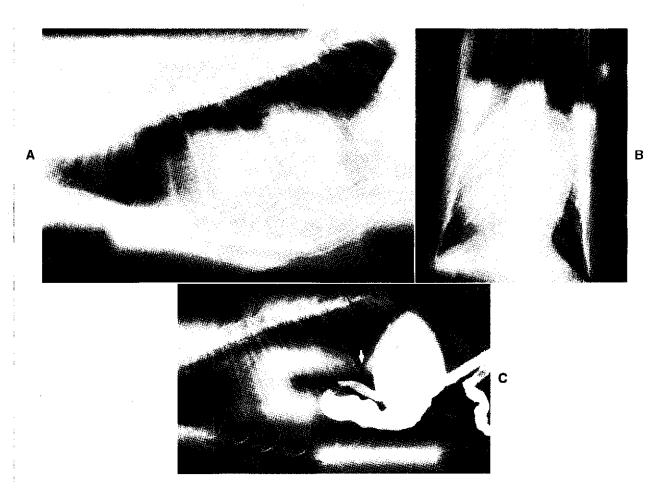


FIG 9-1

Lateral **(A)** and dorsoventral **(B)** radiographs from a 5-year-old male Persian cat with a congenital peritoneopericardial diaphragmatic hernia (PPDH). Note the greatly enlarged cardiac silhouette containing fat, soft tissue, and gas densities as well as tracheal elevation. There is overlap between the cardiac and diaphragmatic borders on both views. Presence of a portion of the stomach and duodenum within the pericardium is evident after barium administration **(C)**; omental fat and liver are also present within the pericardial sac. In **C**, the dorsal pleural fold between pericardium and diaphragm is best appreciated (arrow).



FIG 9-2
Right parasternal short-axis echocardiogram from a female Persian cat with peritoneopericardial diaphragmatic hernia [PPDH]. The pericardium (PERI), indicated by arrows, surrounds liver and omental tissue as well as the heart. LV, Left ventricle.

pathophysiologic signs and clinical presentation can mimic those seen with pericardial effusion. Radiographically, the cardiac silhouette may appear enlarged and deformed. Echocardiography or pneumopericardiography can reveal the diagnosis. Surgical cyst removal, combined with partial pericardiectomy, usually resolves the clinical signs.

Congenital defects of the pericardium itself are extremely rare in dogs and cats; most are incidental postmortem findings. Sporadic cases of partial (usually left-sided) or complete absence of the pericardium are reported. A possible complication of partial absence of the pericardium is herniation of a portion of the heart; this could cause syncope, embolic disease, or sudden death. Echocardiography or angiocardiography may allow antemortem diagnosis.

#### PERICARDIAL EFFUSION

#### **Etiology and Types Of Fluid**

In dogs most pericardial effusions are serosanguineous or sanguineous and are of neoplastic or idiopathic origin. Transudates, modified transudates, and exudates are found occasionally in both dogs and cats.

#### **HEMORRHAGE**

Hemorrhagic effusions are common in dogs. The fluid usually appears dark red, with a packed cell volume (PCV) >7%, a specific gravity >1.015, and a protein concentration >3 g/dl. Cytologic analysis shows mainly red blood cells, but reactive mesothelial, neoplastic, or other cells may be seen.

The fluid does not clot unless hemorrhage was very recent. Neoplastic hemorrhagic effusions are more likely in dogs older than 7 years. Middle-aged, large-breed dogs are most likely to have idiopathic "benign" hemorrhagic effusion.

Hemangiosarcoma (HSA) is by far the most common neoplasm causing hemorrhagic pericardial effusion in dogs; it is uncommon in cats. Hemorrhagic pericardial effusion also occurs in association with various heartbase tumors; pericardial mesotheliomas; malignant histiocytosis (MH); and, rarely, metastatic carcinoma. HSAs (see p. 167) usually arise within the right heart, especially in the right auricular appendage. Chemodectoma is the most common heartbase tumor; it arises from chemoreceptor cells at the base of the aorta. Thyroid, parathyroid, lymphoid, and connective tissue neoplasms also occur at the heartbase. Pericardial mesothelioma develops in some dogs and cats and may mimic idiopathic disease. Lymphoma involving various parts of the heart is seen more often in cats than in dogs. Dogs with MH and pericardial effusion usually have pleural effusion and ascites despite the fact that they do not have cardiac tamponade.

Idiopathic (benign) pericardial effusion is reported most frequently in medium- to large-breed dogs. Golden Retrievers, Labrador Retrievers, and Saint Bernards may be predisposed. Although dogs of any age can be affected, the median age is 6 to 7 years. More cases have been reported in males than females. Mild pericardial inflammation, with diffuse or perivascular fibrosis and focal hemorrhage, is common on histologic exam. Layers of fibrosis suggest a recurrent process in some cases. Constrictive pericardial disease is a potential complication.

Other, less common causes of intrapericardial hemorrhage include left atrial rupture secondary to severe mitral insufficiency (see p. 116), coagulopathy, penetrating trauma (including iatrogenic laceration of a coronary artery during pericardiocentesis), and possibly uremic pericarditis.

#### **TRANSUDATES**

Pure transudates are clear, with a low cell count (usually <1000 cells/µl), specific gravity (<1.012), and protein content (<2.5 g/dl). Modified transudates may appear slightly cloudy or pink tinged. Their cellularity (~1000 to 8000 cells/µl) is still low, but total protein concentration (~2.5-5.0 g/dl) and specific gravity (1.015-1.030) are higher than those of a pure transudate. In some dogs and cats, transudative effusions occur with congestive heart failure (CHF), hypoalbuminemia, PPDH and pericardial cysts, and toxemias that increase vascular permeability (including uremia). These conditions usually are associated with relatively small-volume pericardial effusion; cardiac tamponade is rare.

#### **EXUDATES**

Exudative effusions are cloudy to opaque or serofibrinous to serosanguineous. They typically have a high nucleated cell count (usually much higher than 3000 cells/µl), protein content (often much above 3 g/dl), and specific gravity (>1.015). Cytologic findings are related to the etiology. Exudative pericardial effusions are found only rarely in small animals, except in cats with feline infectious peritonitis (FIP).

Infectious pericarditis is usually related to plant awn migration, bite wounds, or extension of a pleural or mediastinal infection. Various bacteria (aerobic and anaerobic), actinomycosis, coccidioidomycosis, disseminated tuberculosis, and, rarely, systemic protozoal infections have been identified. Sterile exudative effusions are reported with leptospirosis, caninc distemper, and idiopathic pericardial effusion in dogs and with FIP and toxoplasmosis in cats. FIP is the most important cause of symptomatic pericardial effusion in cats. Chronic uremia occasionally causes a sterile, serofibrinous or hemorrhagic effusion.

#### **Pathophysiology**

Fluid accumulation within the pericardial space causes clinical signs when it raises intrapericardial pressure to or above normal cardiac filling pressure. This accumulation impedes venous return and cardiac filling. As long as intrapericardial pressure remains low, cardiac filling and output remain relatively normal. If fluid accumulates slowly, the pericardium may distend enough to accommodate the increased effusate volume at relatively low pressure. However, pericardial tissue is relatively noncompliant. Rapid fluid accumulation or a very large effusion causes a steep rise in intrapericardial pressure, leading to cardiac tamponade. Pericardial fibrosis and thickening further limit the compliance of this tissue.

Pericardial effusion of very large volume may cause clinical signs by virtue of its size, even without overt cardiac

tamponade. Lung and/or tracheal compression can compromise ventilation and stimulate cough; esophageal compression can cause dysphagia or regurgitation.

#### CARDIAC TAMPONADE

Cardiac tamponade develops when pericardial fluid accumulation raises intrapericardial pressure to or above the normal cardiac diastolic pressure. This external compression of the heart progressively limits filling, initially of the right heart, then the left. Cardiac output subsequently falls while systemic venous pressure rises. Pressure in all cardiac chambers and the great veins eventually becomes equilibrated during diastole. Neurohormonal compensatory mechanisms are activated as tamponade develops. Gradual pericardial fluid accumulation results in signs of CHF because of compensatory volume retention and the direct effects of impaired cardiac filling. Manifestations of systemic venous congestion and right-sided CHF (ascites and pleural effusion) usually predominate because of the right heart's thinner wall and low pressures. Pericardial effusion does not typically affect cardiac contractility directly, but reduced coronary perfusion during tamponade can impair both systolic and diastolic function. Low cardiac output, arterial hypotension, and poor organ perfusion can ultimately lead to cardiogenic shock and death.

The rate of pericardial fluid accumulation and the distensibility of the pericardial sac determine whether and how quickly cardiac tamponade develops. Rapid accumulation of even a relatively small volume can raise intrapericardial pressure sharply. A gradual process is implied when the pericardial fluid volume is large. Cardiac tamponade is relatively common in dogs but rare in cats.

Pulsus paradoxus is the term used to describe the exaggerated variation in arterial blood pressure that occurs during the respiratory cycle as a result of cardiac tamponade. During inspiration intrapericardial and right atrial (RA) pressures fall, which facilitates right heart filling and pulmonary blood flow. At the same time, left heart filling is reduced as more blood is held in the lungs and the interventricular septum bulges leftward from the inspiratory increase in right ventricular (RV) filling; consequently, left heart output and systemic arterial pressure decrease during inspiration. The variation in systolic arterial pressure between inspiration and expiration is usually >10 mm Hg in patients with cardiac tamponade and pulsus paradoxus. Pulsus paradoxus is not always discernible using palpation of the femoral pulse.

#### Clinical Features

Clinical findings in patients with cardiac tamponade usually reflect right-sided CHF as well as poor cardiac output. Before obvious ascites develops, possible nonspecific signs include lethargy, weakness, poor exercise tolerance, and inappetence. The history typically includes complaints of weakness, exercise intolerance, abdominal enlargement, tachypnea, syncope, and cough. A history of collapse is more common in dogs with neoplastic disease; dogs without a mass lesion are more



FIG 9-3
Older male Boxer with chronic cardiac tamponade and right-sided congestive heart failure secondary to chemodectoma. The abdomen is greatly distended with ascites; chronic loss of lean body mass is evident along the spine, pelvis, and rib cage.

likely to have obvious ascites. Marked loss of lean body mass occurs in some chronic cases (Fig. 9-3).

Jugular vein distention and/or positive hepatojugular reflux, hepatomegaly, ascites, labored respirations, and weak femoral pulses are common physical examination findings. Pleural effusion and ascites are also common in cats, as well as dogs, with cardiac tamponade. A palpable decrease in arterial pulse strength during inspiration (pulsus paradoxus) might be discernible in some dogs with tamponade. Sinus tachycardia, pale mucous membranes, and prolonged capillary refill time are manifestations of high sympathetic tone. The precordial impulse is weak when the pericardial fluid volume is large. Heart sounds are muffled in patients with moderate to large pericardial effusions. Lung sounds are muffled over the ventral thorax in those with pleural effusion. Although pericardial effusion does not cause a murmur, concurrent cardiac disease may do so. If fluid has rapidly accumulated, acute tamponade can lead to shock and death without obvious signs of pleural effusion, ascites, or radiographic evidence of cardiomegaly. In such cases, jugular venous distention, hypotension, and pulmonary edema may be evident. Infectious pericarditis may be accompanied by fever; rarely, a pericardial friction rub might be heard.

#### **Diagnosis**

A central venous pressure (CVP) above 10 to 12 cm  $H_2O$  is common; normally, CVP is <8 cm  $H_2O$ . CVP measurement is helpful when the jugular veins are difficult to assess or it is unclear whether right heart filling pressure is elevated. Moderate- to large-volume pleural effusion should be drained before CVP measurement, not only to stabilize the patient but also to minimize artifactual CVP elevation.

#### RADIOGRAPHY

Pericardial effusion enlarges the cardiac silhouette (Fig. 9-4). A massive amount of pericardial fluid causes the classic globoid-shaped heart shadow on both radiographic views. Smaller fluid volumes allow various cardiac contours to be identified, especially dorsally. Other findings associated with tamponade include pleural effusion, a distended caudal vena cava, hepatomegaly, and ascites. Pulmonary infiltrates of edema and distended pulmonary veins are seen ocasionally. Some heartbase tumors cause tracheal deviation or a soft-tissue mass effect. Metastatic lung lesions are common in dogs with hemangiosarcoma.

When used, fluoroscopy demonstrates diminished to absent motion of the cardiac shadow because of the fluid surrounding the heart. Angiocardiography is used only rarely now to evaluate patients with pericardial effusion and cardiac tumors; it typically reveals increased endocardialto-pericardial distance. Cardiac neoplasms can cause displacement of normal structures, filling defects, and vascular "blushing" (opacification of excessive, abnormal tumorassociated vessels). Pneumopericardiography has also been replaced by echocardiography. Pneumopericardiography uses carbon dioxide or air injected into the drained pericardial sac to outline the heart, but it is rarely used these days. Radiographs are taken from different orientations, but the left lateral and dorsoventral views are most helpful. These views allow the injected gas to outline the right atrial and heartbase areas, respectively, where tumors are most common.

#### **ELECTROCARDIOGRAPHY**

Although there are no pathognomonic electrocardiographic (ECG) findings, the following abnormalities are suggestive of pericardial effusion: small amplitude QRS complexes (<1 mV in dogs), electrical alternans, and ST segment elevation (epicardial injury current). Electrical alternans is a recurring alteration in the size of the QRS complex (or sometimes the T wave) with every other beat (Fig. 9-5). It results from the back-and-forth swinging motion of the heart within the pericardium. Electrical alternans is most likely to be seen in patients with large-volume pericardial effusion; it may be most evident at heart rates between 90 and 140/min and/or in the standing position. Sinus tachycardia is common with cardiac tamponade. Atrial or ventricular tachyarrhythmias may also occur.

#### **ECHOCARDIOGRAPHY**

Echocardiography is highly sensitive for detecting pericardial fluid, and it is the preferred diagnostic modality if radiographic changes are equivocal. Because fluid is sonolucent, pericardial effusion appears as an echo-free space between the bright parietal pericardium and the epicardium (Fig. 9-6). Abnormal cardiac wall motion and chamber shape and intrapericardial or intracardiac mass lesions can also be imaged. With large-volume pericardial effusion, the heart may appear to swing back and forth within the pericardial sac. Cardiac tamponade is manifested by diastolic compression/collapse of the right atrium and sometimes the

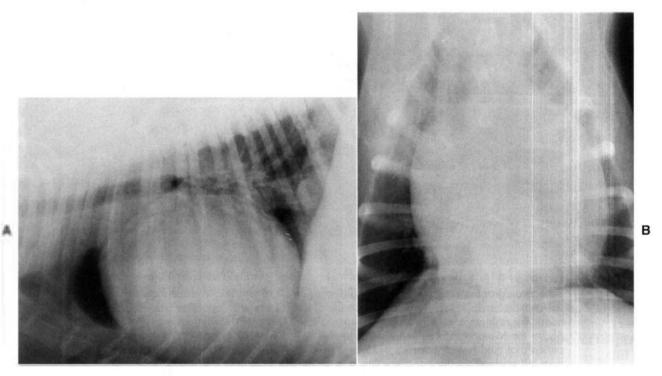


FIG 9-4
Lateral (A) and dorsoventral (B) radiographs from a mixed-breed dog with large pericardial effusion. Note globoid shape of cardiac silhouette and distended caudal vena cava (A).

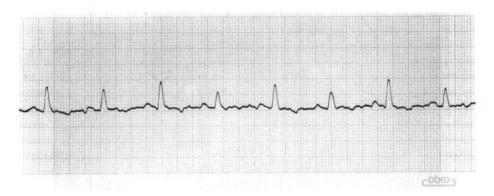


FIG 9-5
Electrical alternans is evident on this lead II electrocardiogram from a 10-year-old male Bulldog with a large pericardial effusion. Note also the small voltage QRS complexes and sinus tachycardia (heart rate about 170 beats/min).

right ventricle (Fig. 9-7). It must be remembered that the volume of effusion is not the main determinant of hemodynamic compromise but rather the intrapericardial pressure. The RV and RA walls are often well visualized and may appear hyperechoic because of the surrounding fluid. Better visualization of the heartbase and mass lesions is generally obtained before pericardiocentesis is performed. Careful evaluation of all portions of the right atrium and auricle, right ventricle, ascending aorta, and pericardium itself is important to screen for neoplasia. The left cranial parasternal (and transesophageal) transducer positions are especially useful. Some mass lesions are difficult to visualize.

Mesothelioma may not cause discrete mass lesions and therefore may be indistinguishable from idiopathic pericardial effusion.

Sometimes pleural effusion, a markedly enlarged left atrium, a dilated coronary sinus, or persistent left cranial vena cava can be confused with pericardial effusion. Careful scanning from several positions helps in differentiating these conditions. Identification of the parietal pericardium in relation to the echo-free fluid helps differentiate pleural from pericardial effusion. Because the pericardium is a relatively strong ultrasound reflector, by progressively dampening the returning echo signals, pericardial echos are seen to be the

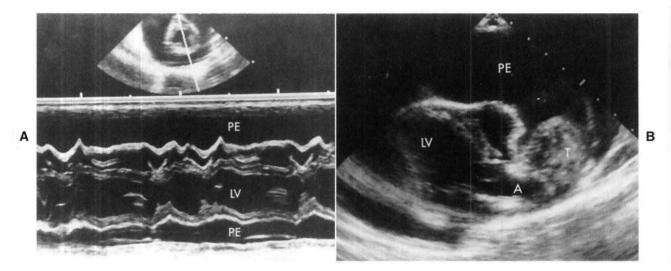


FIG 9-6

Echocardiographic examples of pericardial effusion. **A,** Short-axis M-mode view at mitral valve and chordal levels. Large echo-free (fluid) spaces are seen on either side of the heart; the right ventricular wall is clearly visualized. The small two-dimensional image above the M-mode shows the heart (transected by the M-mode cursor line) surrounded by pericardial fluid (which appears black on the image). **B,** Long-axis two-dimensional view from left parasternal position depicting a large heartbase tumor and pericardial effusion in a Schnauzer. *PE*, Pericardial effusion; *T,* tumor; *LV*, left ventricle; *A,* aorta.

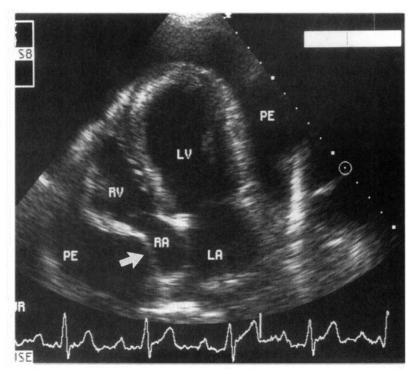


FIG 9-7

Diastolic compression of the right atrial wall (arrow) is evident in this left caudal four-chamber echocardiogram from a 3-year-old female Saint Bernard with cardiac tamponade. LA, Left atrium; LV, left ventricle; PE, pericardial effusion; RA, right atrium; RV, right ventricle.

last to disappear. Most pericardial fluid accumulates near the cardiac apex because the pericardium adheres more tightly to the heartbase; there is usually little fluid behind the left atrium. Furthermore, evidence of collapsed lung lobes or pleural folds can often be seen within pleural effusion.

#### **CLINICOPATHOLOGIC FINDINGS**

Hematologic and biochemical test results are generally nonspecific. The complete blood count (CBC) may suggest inflammation or infection. Cardiac HSA may be associated with a regenerative anemia, increased numbers of nucleated red blood cells and schistocytes, and thrombocytopenia. Mild hypoproteinemia is seen in some cases of pericardial effusion. Cardiac troponin concentration or enzyme activities may be increased as a result of ischemia or myocardial invasion; mild increases in liver enzyme activities and prerenal azotemia may occur secondary to heart failure. Pleural and peritoneal fluids in dogs and cats with cardiac tamponade are usually modified transudates.

Pericardiocentesis (discussed in the next section) usually yields a hemorrhagic effusion; occasionally the fluid is suppurative. Samples are submitted for cytologic analysis and saved for possible bacterial (or fungal) culture. Nevertheless, differentiation of neoplastic effusions from benign hemorrhagic pericarditis is usually impossible on the basis of cytology alone. Reactive mesothelial cells within the effusion may closely resemble neoplastic cells; furthermore, chemodectomas and HSAs may not shed cells into the effusion. Therefore identifying a mass lesion with echocardiography is helpful for diagnosis. The effusions in patients with lymphoma or MH typically are consistent with a modified transudate. Neoplastic cells usually are easily identified in dogs and cats with lymphoma and in dogs with MH. Many neoplastic (and other non-inflammatory) effusions have a pH of 7.0 or greater, whereas inflammatory effusions generally have lower pH. However, there appears to be too much overlap for pericardial pH to be used as a reliable discriminator. Pericardial fluid culture is performed if cytology and pH suggest an infectious or inflammatory cause. In some patients fungal titers (e.g., coccidioidomycosis) or other serologic tests are helpful. It is currently unclear whether analysis of pericardial fluid for cardiac troponins or other substances will allow better differentiation of the underlying etiology.

#### Treatment and Prognosis

It is important to differentiate cardiac tamponade from other causes of right-sided CHF because the treatment is very different. Positive inotropic drugs do not ameliorate the signs of tamponade; diuretics and vasodilators can further reduce cardiac output and exacerbate hypotension and shock. Pericardiocentesis (discussed in the next section) is the immediate treatment of choice, and it also provides diagnostic information. Most signs of CHF resolve after pericardial fluid is removed. A dose or two of a diuretic may be useful after pericardiocentesis in some animals. Pericardial effusions secondary to other diseases that cause CHF, congenital malformations, or hypoalbuminemia do not usually

cause tamponade and often resolve with management of the underlying condition.

Dogs with idiopathic pericardial effusion are initially treated conservatively by pericardiocentesis. After an infectious cause is ruled out by pericardial fluid culture or cytologic analysis, a glucocorticoid is often used (e.g., oral prednisone, 1 mg/kg/day, tapered over 2-4 weeks); however, its efficacy in preventing recurrent idiopathic pericardial effusion is unknown. Sometimes a 1- to 2-week course of a broad-spectrum antibiotic is used concurrently. Periodic reevaluation of these dogs by radiography or echocardiography is advised to detect recurrence. Apparent recovery occurs after one or two pericardial taps in about half of affected dogs. Cardiac tamponade recurs after a variable time span (days to years) in other cases. Some cases of recurrent effusion are caused by mesothelioma, MH, or other neoplasia, which may become evident on repeated echocardiographic exam.

Recurrent effusion that does not respond to repeated pericardiocenteses and antiinflammatory therapy is usually treated by subtotal pericardiectomy. Removal of the pericardium ventral to the phrenic nerves allows pericardial fluid drainage to the larger absorptive surface of the pleural space. The less invasive technique of thoracoscopic partial pericardiectomy has also been used successfully to treat idiopathic and some cases of neoplastic pericardial effusion; biopsy samples of the mass or masses (if identified) can be obtained through thoracoscopy. Lateral and subxiphoid approaches have been described. Percutaneous balloon pericardiotomy also appears to be an effective and even less invasive option for some cases. This procedure is performed under general anesthesia with fluoroscopic guidance. It involves placing a percutaneous sheath introducer through the chest wall into the pericardial space, then inserting a large balloon dilation catheter. The sheath is adjusted so that the balloon can be positioned across the pericardial membrane; as the balloon is inflated, it stretches the hole in the parietal pericardium. There is some concern that adhesions developing around a small pericardiotomy opening may result in fluid reaccumulation or increased risk of constrictive pericarditis.

Neoplastic pericardial effusions are also initially drained to relieve cardiac tamponade. Therapy may involve attempted surgical resection (depending on tumor size and location) or surgical biopsy, a trial of chemotherapy (based on biopsy or clinicopathologic findings), or conservative therapy until episodes of cardiac tamponade become unmanageable. Surgical resection of HSA is often not possible because of the size and extent of the tumor. Small tumors involving only the tip of the right auricle have been successfully removed; use of a pericardial patch graft may allow resection of larger masses involving the lateral RA wall. However, auriculectomy alone rarely results in prolonged long-term survival. Partial pericardiectomy may prevent the recurrence of tamponade. The increased potential for tumor dissemination throughout the thoracic cavity does not appear to affect survival time, compared with pericardiocentesis alone, in dogs with HSA or mesothelioma. The prognosis in dogs with RA HSA treated with surgery alone or in those in which treatment is declined by the owners is poor (median survival of 2-3 weeks); most dogs with atrial HSA have objective responses to multiagent chemotherapy (VAC protocol) and survival times of 4 to 8 months. Survival time in dogs with mesothelioma may be slightly longer than in those with HSA, but the overall prognosis is poor.

Heartbase tumors (e.g., chemodectoma) tend to be slow growing and locally invasive and have a low metastatic potential. Partial pericardiectomy may prolong survival for years. Percutaneous balloon pericardiotomy may also be an effective palliative procedure. Because of local invasion, complete surgical resection is rarely possible; attempts at aggressive resection often result in severe bleeding and death. However, small, well-defined masses may be completely resectable. Surgical biopsy is indicated if chemotherapy is contemplated. Effusion secondary to myocardial lymphoma, usually easily diagnosed cytologically, often responds to pericardiocentesis and chemotherapy.

Infectious pericarditis should be treated aggressively with appropriate antimicrobial drugs, as determined by microbial culture and sensitivity testing. Surgical therapy is likely to be more effective than continuous drainage with an indwelling pericardial catheter, and it also allows removal of penetrating foreign bodies. The prognosis is guarded. Even with successful elimination of infection, epicardial and pericardial fibrin deposition may lead to constrictive pericardial disease.

Pure hemorrhage into the pericardial space, whether the result of trauma, rupture of the left atrium, or a systemic coagulopathy, should be removed if signs of cardiac tamponade exist. Only enough blood to control signs of tamponade should be removed because continued drainage may predispose to further bleeding. The remaining blood is usually resorbed through the pericardium (autotransfusion). Surgery may be needed to stop continued bleeding or remove large clots. Dogs that survive an initial episode of intrapericardial bleeding from rupture of the left atrium still have a guarded to poor prognosis because of recurrent tearing of the left atrium. Animals with intrapericardial hemorrhage of unclear cause should be evaluated for a coagulation disorder. When trauma-induced intrapericardial hemorrhage persists in an animal with normal hemostasis, surgical exploration is indicated.

#### Complications

Complications of diseases causing pericardial effusion relate to (1) sequelae of the fluid accumulation itself (e.g., cardiac tamponade and compression of surrounding structures [lung, esophagus, trachea]), (2) immediate effects of associated inflammatory processes (e.g., arrhythmias, local and systemic effects of infectious agents, further fluid formation), (3) pericardial fibrosis and subsequent constrictive pericarditis, (4) sequelae of neoplastic processes (e.g., further bleeding, metastases, local invasion and obstruction, seeding of the pleura, loss of function), and (5) complications of pericardiocentesis (discussed in the next section). Overly aggressive surgical attempts to remove cardiac tumors or the

entire pericardial sac can be fatal, and partial pericardiectomy may enhance intrathoracic dissemination of certain tumors such as mesothelioma and carcinoma.

#### **PERICARDIOCENTESIS**

Pericardiocentesis should be done immediately in animals with cardiac tamponade. Administration of diuretics or vasodilators without pericardiocentesis may cause further hypotension and cardiogenic shock. Pericardiocentesis is a relatively safe procedure when performed carefully. Removal of even a small volume of pericardial fluid can markedly decrease intrapericardial pressure in animals with tamponade.

Pericardiocentesis is usually done from the right side to minimize the risk of trauma to the lung (via the cardiac notch) and major coronary vessels (located mostly on the left). The need for sedation depends on the clinical status and temperament of the animal. The animal is usually placed in left lateral or sternal recumbency for more secure restraint, especially if the animal is weak or excitable. Sometimes needle pericardiocentesis can be successfully performed on the standing animal, but the risk of injury increases if the patient suddenly moves. An elevated echocardiography table with a large cutout can also be used with good success; the animal is placed in right lateral recumbency, and the tap is performed from underneath. An advantage to this method is that fluid moves to the right side with gravity; however, if adequate space is not available for wide sterile skin preparation or needle/catheter manipulation, this approach is not advised. Echo guidance can be used but is not necessary unless the effusion is of very small volume or appears compartmentalized.

A variety of equipment can be used for pericardiocentesis. A butterfly needle/catheter (19- to 21-gauge) or appropriately long hypodermic or spinal needle attached to extension tubing is adequate in emergency situations. An over-theneedle catheter system is a safer alternative because it reduces the risk of cardiopulmonary laceration during fluid aspiration. The catheter is chosen according to patient size (e.g., 12- to 16-gauge, 4- to 6-inch long catheter for large dogs, down to 18- to 20-gauge, 11/2- to 2-inch long catheter for small dogs or cats). A few extra small side holes may be smoothly cut (with sterile scissors) near the tip of larger catheters to increase fluid removal rate. During initial catheter placement the extension tubing is attached to the needle stylet. After the catheter is advanced into the pericardial space, the extension tubing is reattached directly to the catheter. With all methods, a three-way stopcock is placed between the tubing and a collection syringe.

An ECG monitor should be in place during pericardiocentesis because needle/catheter contact with the heart commonly induces ventricular arrhythmias. The skin is shaved over a wide area of the right precordium (from about the third to seventh intercostal spaces and from sternum to costochondral junction) and surgically prepared. Sterile gloves and aseptic technique are used for the procedure. The puncture site is located by palpating to identify the point at which the cardiac impulse feels strongest (usually between the fourth and sixth ribs just lateral to the sternum). Local anesthesia is necessary when using large catheters and recommended for needle pericardiocentesis. Lidocaine (2%) is infiltrated with sterile technique at the skin puncture site, into underlying intercostal muscles, and into the pleura. A small stab incision is made in the skin to allow catheter entry.

Intercostal vessels are located just caudal to each rib and must be avoided when entering the chest. Once the needle has penetrated the skin, the operator's assistant should apply gentle negative pressure to the attached syringe as the operator slowly advances the needle toward the heart. It is sometimes helpful to aim the tip of the needle toward the animal's opposite shoulder. The tubing is observed so that fluid will be seen as soon as it is aspirated. Pleural fluid (usually straw colored) may enter the tubing first and is drained as much as possible. The pericardium creates increased resistance to needle advancement and may produce a subtle scratching sensation. Gentle pressure is used to advance the needle through the pericardium. A loss of resistance may be noted with needle penetration, and fluid aspirated into the tubing usually appears dark red. If the needle comes into contact with the heart, a marked scratching or tapping sensation is usually felt, the needle may move with the heartbeat, and ventricular premature complexes are often provoked. The needle should be retracted slightly if cardiac contact occurs. It is important to avoid excessive needle motion within the chest. When a catheter system is used, after the needle/stylet is well within the pericardial space, the catheter is advanced, the stylet removed, and the extension tubing attached to the catheter. Initial fluid samples are saved for cytologic exam and possible culture, and then as much fluid as possible is aspirated.

Pericardial effusion usually appears quite hemorrhagic. It can be distressing to see dark, bloody fluid being aspirated from near the heart, but pericardial fluid can be differentiated from intracardiac blood in several ways. Unless the fluid is caused by very recent pericardial hemorrhage, it will not clot. (A few drops can be placed on the table or into a serum tube to check.) The PCV of pericardial fluid is usually much lower than that of peripheral blood (except in some dogs with HSA); also, the supernatant is xanthochromic (yellow tinged) when spun in a hematocrit tube. As the pericardial fluid is drained, the animal's ECG complexes increase in amplitude, tachycardia diminishes, and the patient often takes a deep breath and appears more comfortable.

#### Complications

Complications of pericardiocentesis include (1) cardiac injury or puncture causing arrhythmias (the most common complication, although usually self-limiting when the needle is withdrawn), (2) lung laceration causing pneumothorax and/or hemorrhage, (3) coronary artery laceration with myocardial infarction or further bleeding into the pericardial space, and (4) dissemination of infection or neoplastic cells into the pleural space.

#### CONSTRICTIVE PERICARDIAL DISEASE

#### **Etiology and Pathophysiology**

Constrictive pericardial disease is diagnosed occasionally in dogs but only rarely in cats. This condition occurs when thickening and scarring of the visceral and/or parietal pericardium restrict ventricular diastolic expansion and prevent normal cardiac filling. Both ventricles are affected. Usually the entire pericardium is involved symmetrically. Fusion of parietal and visceral pericardial layers obliterates the pericardial space in some cases. In others the visceral layer (epicardium) alone is involved. A small amount of pericardial effusion (constrictive-effusive pericarditis) may be present.

Increased fibrous connective tissue and variable amounts of inflammatory and reactive pericardial infiltrates are seen on histopathologic exam. Although the etiology of constrictive pericardial disease is often unknown, acute inflammation with fibrin deposition and possibly varying degrees of pericardial effusion are thought to precede its development. Some cases in dogs are attributable to recurrent idiopathic hemorrhagic effusion, infectious pericarditis (resulting from actinomycosis, mycobacteriosis, coccidioidomycosis), a metallic foreign body in the pericardium, tumors, and idiopathic osseous metaplasia and/or fibrosis of the pericardium.

In advanced constrictive pericardial disease, ventricular filling is limited essentially to early diastole, before ventricular expansion is abruptly curtailed. Any further ventricular filling is accomplished only at high venous pressures. Compromised filling reduces cardiac output, and compensatory mechanisms of heart failure cause fluid retention, tachycardia, and vasoconstriction.

#### **Clinical Features**

Middle-aged, large- to medium-breed dogs are most often affected. Males and German Shepherd Dogs may be at higher risk. Some dogs have a history of pericardial effusion. Clinical signs of right-sided CHF predominate. Abdominal distention (ascites), tachypnea or labored breathing, tiring, syncope, weakness, and weight loss are common complaints. These signs may develop over weeks to months. Ascites and jugular venous distention are the most consistent clinical findings, as in dogs with cardiac tamponade. Weakened femoral pulses and muffled heart sounds are also typical. A diastolic pericardial knock sound, resulting from abrupt deceleration of ventricular filling in early diastole, has been described but is not often identified in dogs. A systolic murmur or click, probably caused by valvular disease rather than the pericardial pathology, or a diastolic gallop sound may be heard.

#### **Diagnosis**

The diagnosis of constrictive pericardial disease may be difficult. Typical radiographic findings include mild to moderate cardiomegaly, pleural effusion, and caudal vena cava distention. Reduced cardiac motion may be evident on fluo-

roscopy. Echocardiographic changes in dogs with constrictive pericardial disease may be subtle; suggestive findings include diastolic flattening of the left ventricular freewall and abnormal septal motion. The pericardium may appear thickened and intensely echogenic, but differentiating this from normal pericardial echogenicity may be impossible. Possible ECG abnormalities include sinus tachycardia, P-wave prolongation, and small QRS complexes.

A CVP >15 mm Hg is common. Intracardiac hemodynamic measurements are most useful diagnostically. In addition to high mean atrial and diastolic ventricular pressures, the atrial pressure waveform shows a prominent y descent (during ventricular relaxation). This is in contrast to cardiac tamponade, wherein the y descent is diminished. During tamponade, ventricular diastolic expansion immediately raises intrapericardial pressure and impairs caval flow into the right atrium, thus preventing the normal early diastolic decrease in CVP (y descent), although flow into the right atrium (and x descent on atrial waveform) continues during ventricular contraction. With constrictive pericardial disease, filling pressure is low only in early diastole (during the time of y descent). Another classic finding with constrictive pericardial disease is an early diastolic dip in ventricular pressure, followed by a mid-diastolic plateau, but this is not consistently seen in dogs. Results of angiocardiography may be normal, or they may show atrial and vena caval enlargement with increased endocardial-pericardial distance.

#### Treatment and Prognosis

Therapy for constrictive pericardial disease consists of surgical pericardiectomy. This is more successful when only the parietal pericardium is involved. Constrictive pericardial disease involving the visceral layer requires epicardial stripping. This procedure increases the surgical difficulty and associated complications. Pulmonary thrombosis is reportedly a common postoperative complication and can be lifethreatening. Tachyarrhythmias are another complication of surgery. In the postoperative period, a diuretic and possibly an angiotensin-converting enzyme inhibitor (ACEJ) may be helpful. Positive inotropic and vasodilating drugs are not usually indicated. Constrictive pericardial disease is progressive and, without successful surgical intervention, ultimately fatal.

#### CARDIAC TUMORS

#### **Etiology and Pathophysiology**

Echocardiography has made the antemortem diagnosis of cardiac tumors more common, although the overall prevalence of such neoplasms is low. Some cardiac tumors cause severe clinical signs, whereas others are diagnosed fortuitously. Dogs with cardiac tumors tend to be middle-aged and older. More than 85% of affected dogs are between 7 and 15 years of age; however, very old dogs (>15 years) have a surprisingly low prevalence. Reproductive status influences the relative risk for cardiac tumors in dogs, despite a similar frequency of occurrence in males and females overall. Neutered dogs have a greater relative risk, especially spayed females, which have a risk that is four to five times greater compared with that of intact females. Intact and neutered males also have greater risk than intact females. Certain breeds of dog have a higher prevalence of cardiac tumor compared with the general population (Table 9-1). The age distribution of cats with cardiac tumors is different from that of dogs; about 28% are 7 years old or younger. It is unknown whether reproductive status affects relative risk for cardiac tumors in cats.

The most common cardiac tumor in dogs is HSA. Most are located in the right atrium and/or right auricle; some also infiltrate the ventricular wall. HSAs usually are associated with hemorrhagic pericardial effusion and cardiac tampon-



TABLE 9-1 Dog Breeds with High Prevalence of Cardiac Tumors

BREED	# WITH TUMOR	# IN DATABASE	RELATIVE RISK	95% CI
Saluki	6	401	7.75	3.92-15.38
French Bulldog	3	215	<i>7.</i> 19	2.72-19.23
Irish Water Spaniel	2	168	6.13	1.81-20.83
Flat-Coated Retriever	4	534	3.85	1.54-9.62
Golden Retriever	215	32,940	3.73	3.26-4.27
Boxer	52	8,496	3.22	2.47-4.18
Afghan Hound	12	2,080	2.97	1,72-5.10
English Setter	21	3,796	2.86	1.89-4.31
Scottish Terrier	16	3,290	2.50	1.55-4.03
Boston Terrier	25	5,225	2.47	1.68-3.62
Bulldog	24	5,580	2.22	1.49-3.29
German Shepherd Dog	129	37,872	1.81	1. <b>52</b> -2.1 <i>7</i>

Modified from Ware WA, Hopper DL: Cardiac tumors in dogs: 1982-1995, J Vet Intern Med 13:95, 1999. CI, Confidence interval.

ade (see p. 158). Metastases are common by the time of diagnosis. Golden Retrievers, German Shepherd Dogs, Afghan Hounds, Cocker Spaniels, English Setters, and Labrador Retrievers, among others, are at higher risk for this tumor.

Masses at the heartbase are the second most frequently reported cardiac tumor in dogs. They are usually neoplasms of the chemoreceptor aortic bodies (chemodectoma, aortic body tumors); ectopic thyroid or parathyroid, or mixed-cell-type tumors also occur here. Heartbase tumors tend to be locally invasive around the root of the aorta and surrounding structures; metastases to other organs occur rarely. Chemodectomas are reported more frequently in brachycephalic dogs (specifically Boxers, Boston Terriers, and Bull-dogs) but affect individuals of other breeds as well. Clinical signs associated with heartbase tumors are usually related to pericardial effusion and cardiac tamponade.

Mesothelioma occurs sporadically; there may be geographical variation in its prevalence. Other primary tumors involving the heart are rare in dogs but include myxoma, various types of sarcoma, and other neoplasms. Most cases involve right-heart structures. Metastatic tumors, including lymphoma, other sarcomas, and various carcinomas, may involve the heart as well. MH may involve the heart or pericardium; most affected dogs are either Golden Retrievers, Labrador Retrievers, Rottweilers, or Greyhounds. Mild pericardial effusion, without overt signs of cardiac tamponade, co-exists with pleural and abdominal effusion.

Lymphoma is the most common cardiac tumor in cats. Various (mostly metastatic) carcinomas are the next most common cardiac neoplasms in cats. HSA is uncommon; other tumors (such as aortic body tumor, fibrosarcoma, rhabdomyosarcoma) are reported only rarely in cats.

Cardiac tumors cause several pathophysiologic abnormalities, depending on their location and size. Ultimately, the patient's clinical signs can be referred to one or a combination of these. Many tumors impede cardiac filling by causing pericardial effusion and cardiac tamponade (discussed earlier). An intrapericardial mass can itself externally compress the heart as well as cause pericardial effusion. Alternatively, a tumor that grows in an intracardiac location can physically obstruct cardiac inflow or outflow. Myocardial tumor infiltration or secondary ischemia can disrupt the cardiac rhythm and impair contractility. If the tumor is small or has not yet markedly impaired cardiac function, clinical signs may be absent.

#### **Clinical Features**

Signs of right-sided CHF result from blood flow obstruction within the right atrium or ventricle or from cardiac tamponade. Syncope, weakness associated with exertion, and other low output signs also result from cardiac tamponade, blood flow obstruction, arrhythmias, or impaired myocardial function secondary to cardiac tumors. Tachyarrhythmias of any type may also occur; intracardiac conduction disturbances sometimes result from tumor infiltration. Lethargy or collapse may relate to bleeding tumors (e.g., HSA) present in extracardiac locations as well.

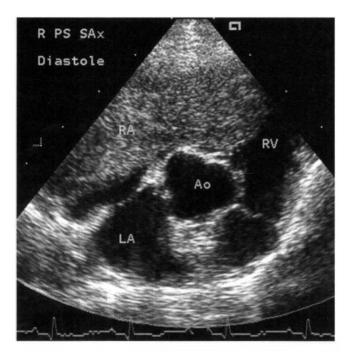
Auscultation findings vary. Arrhythmias or muffled heart sounds (if large pericardial effusion is present) are common. Occasionally a murmur is caused by neoplastic obstruction of intracardiac blood flow, but murmurs associated with unrelated disease (e.g., degenerative mitral regurgitation) are more common. Auscultation findings may be normal.

#### Diagnosis

Radiographic findings are also quite variable. The cardiac silhouette may be normal or show an unusual bulge, a mass effect adjacent to the heart, or a globoid cardiac silhouette compatible with pericardial effusion. Intrapericardial masses are obscured by pericardial effusion. Other radiographic findings that occur secondary to impaired cardiac filling include pleural effusion, evidence of pulmonary edema, widening of the caudal vena cava (and/or pulmonary veins), hepatomegaly, and ascites. Dorsal deviation of the trachea and increased perihilar opacity are seen in some dogs with heartbase tumors. Evidence of pulmonary metastases is found with some primary or secondary (metastatic) cardiac neoplasms.

ECG findings sometimes show abnormalities suggesting the location and sequelae of the underlying disease, such as chamber enlargement, pericardial effusion, and various arrhythmias. Echocardiography can depict cardiac masses and determine the presence or absence of pericardial effusion as well as secondary changes in cardiac chamber size, shape, and ventricular function. Doppler techniques allow assessment of associated blood flow abnormalities. Heartbase tumors that extend into the pericardial space are easier to see when there is pericardial effusion, just as intracardiac masses are accentuated by the echolucent intracardiac blood surrounding them (Fig. 9-8). The left cranial parasternal transducer position may be especially useful in evaluating the ascending aorta, right auricle, and surrounding structures. Echocardiographic assessment of the tumor's location, size, attachment (pedunculated or broad based), and extent (superficial or deeply invading adjacent myocardium) may help in determining whether surgical resection or biopsy is possible. Visualizing a suspected mass lesion in more than one echocardiographic plane helps verify it and prevent the misinterpretation of artifacts.

Pericardial fluid analysis is recommended, although definitive diagnosis of neoplasia cannot usually be made on the basis of cytologic findings alone (see p. 163). Cardiac lymphoma or MH is more likely to be diagnosed on pericardial fluid cytology. Nevertheless, visualization of a cardiac mass using echocardiography, computed tomography, pneumopericardiography, angiography, or another modality is usually necessary for diagnosis. Hematologic and serum biochemical tests are generally nonspecific in dogs and cats with cardiac tumors. Cardiac enzyme activities or circulation troponin concentrations may be high because of ischemia or myocardial invasion; mild increases in serum alanine aminotransferase activity and azotemia may occur with CHF. HSA is often associated with a regenerative anemia, increased number of nucleated red blood cells and schistocytes, leuko-



#### FIG 9-8

Right parasternal short-axis echocardiogram from a 16-yearold Cocker Spaniel and Poodle mix with ascites and weakness. A large right atrial tumor extends across the tricuspid orifice into the ventricle in this diastolic frame. Pericardial effusion was not present in this dog. Ao, Aorta; LA, left atrium; RA, right atrium; RV, right ventricle.

cytosis, and thrombocytopenia. If present, pleural and peritoneal fluids are usually modified transudates.

#### **Treatment and Prognosis**

Unfortunately, there are few good long-term options in most patients with a heart tumor. Cardiac tamponade is managed when it occurs (see p. 163). Conservative therapy (pericardiocentesis as needed, possibly with glucocorticoid administration to decrease inflammation) is used in some animals. Partial pericardiectomy or pericardiotomy may be helpful in animals with recurrent tamponade.

Surgical tumor resection may be possible depending on the location, size, and invasiveness of the mass. Tumors involving only the tip of the right auricular appendage or a pedunculated mass in a surgically accessible location are more likely to be resectable. Intracardiac masses within the right side of the heart might be reached using venous inflow occlusion techniques and rapid cardiotomy; however, surgical access to lesions on the left side of the heart and large or medially attached masses in the right heart generally requires cardiopulmonary bypass.

Surgical biopsy of a nonresectable mass may be helpful if chemotherapy is being contemplated. Although many cardiac tumors appear to be fairly unresponsive to chemotherapy, some are treated with short-term success. Some cardiac hemangiosarcomas respond to vincristine, doxorubicin, and cyclophosphamide combination chemotherapy for 4 to 8 months. Lymphoma and MH should be treated using standard protocols.

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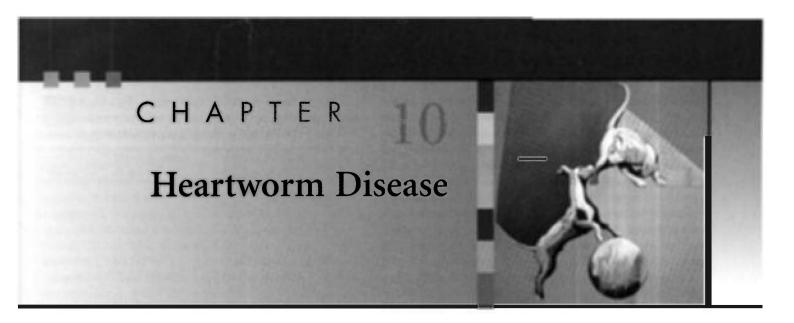
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#### CHAPTER OUTLINE

#### GENERAL CONSIDERATIONS

Heartworm Life Cycle

Tests for Heartworm Disease

#### HEARTWORM DISEASE IN DOGS

Pulmonary Hypertension Without Heartworm Disease

Radiography

Electrocardiography

Echocardiography

Clinicopathic Findings

Pretreatment Evaluation

Adulticide Therapy in Dogs

**Pulmonary Complications** 

Right-sided Congestive Heart Failure

Caval Syndrome

Microfilaricide Therapy

Heartworm Prevention

#### HEARTWORM DISEASE IN CATS

Tests for Heartworm Disease in Cats

Radiography

Echocardiography

Electrocardiography

Other Tests

Medical Therapy and Complications

Surgical Therapy

Microfilaricide Therapy

#### GENERAL CONSIDERATIONS

#### **HEARTWORM LIFE CYCLE**

The heartworm (Dirofilaria immitis) is transmitted by various species of mosquitoes, which act as its obligate intermediate host. A mosquito initially ingests the microfilariae, or first-stage larvae ( $L_1$ ), which circulate in the blood of an infected host animal. The  $L_1$  develops into an  $L_2$  and then enters the infective  $L_3$  stage within the mosquito over a period of approximately 2 to 2.5 weeks. Infective larvae enter

the new host when the mosquito takes another blood meal.  $L_3$  larvae migrate subcutaneously within the new host, molting into an  $L_4$  stage within 9 to 12 days, and then entering the  $L_5$  stage. The juvenile  $L_5$  worms enter the vasculature about 100 days after infection, where they migrate preferentially to the peripheral pulmonary arteries of the caudal lung lobes. It takes at least 5 and usually more than 6 months before these worms develop into adults, at which time gravid females release microfilariae and the infection becomes patent.

Microfilariae passed to another animal by blood transfusion or across the placenta do not develop into adult worms because the mosquito host is required to complete the parasite's life cycle. Therefore puppies younger than 6 months of age that have circulating microfilariae most likely received them transplacentally and do not have patent heartworm disease (HWD).

HWD is widespread throughout the United States, especially along the eastern and gulf coasts and in the Mississippi River valley. Sporadic cases occur in other areas of the country and Canada; the disease is prevalent in other regions of the world as well. Heartworm transmission is limited by climate. An average daily temperature of >64° F for about a month is needed for the  $L_1$  larvae to mature within a mosquito to the infective stage. Heartworm transmission peaks during July and August in temperate regions of the Northern Hemisphere.

Dogs and other canids are the preferred host species. Although cats are also affected by HWD, they are more resistant to infection than dogs. The overall prevalence of heartworm disease in cats is thought to be 5% to 20% of that in dogs in the same geographic area. Reported prevalences range from 0% to >16%. In the United States, cases have been identified in most of the midwest and eastern states and in California.

#### **TESTS FOR HEARTWORM DISEASE** Serologic Tests

**Antigen tests.** Adult heartworm antigen (Ag) tests are recommended as the main screening test for HWD in dogs.

Currently available Ag test kits are highly accurate. Because monthly heartworm preventive drugs promote occult infections by virtually eliminating circulating microfilariae, Ag testing provides higher overall sensitivity for diagnosing HWD. Circulating Ag is usually detectable by about 6.5 to 7 months after infection but not sooner than 5 months. There is no reason to test puppies younger than 7 months. Testing of adults is recommended at about 7 months after the preceding transmission season. Depending on the climate, monthly heartworm prophylaxis may have been started (or continued) before that time.

Commercially available test kits are immunoassays that detect circulating heartworm Ag from the adult female reproductive tract. Most are enzyme-linked immunosorbent assays (ELISAs), although hemagglutination and immunochromatographic test methods also are available. These tests are generally very specific and have a good sensitivity. Positive results are consistently obtained when at least three female worms 7 to 8 months or older are present. Most kits do not detect infections less than 5 months old, and male worms are not detected. Most serum/plasma kits often can identify infections with one live female worm. Microwellformat ELISA tests in general are slightly more sensitive than the rapid assay, membrane-format tests. Of the latter the SNAP test (IDEXX Laboratories, Westbrook, Maine) reportedly is more sensitive for detecting infections with 1 or 2 female worms. A weak positive or ambiguous test result may be rechecked using a different test kit or repeated after a short time with the same type of kit; microfilaria testing and chest radiographs can also help determine whether infection is present. A false-positive Ag test result can usually be traced to a technical error. False-negative results may occur with a low worm burden, immature female worms only, male unisex infection, or a cold test kit. Because the adult worm burden is low in cats and there is greater probability of male unisex infections, false-negative test results are more likely in this species.

Antibody tests. Heartworm antibody tests are marketed for cats. The ELISA antibody (Ab) tests use either recombinant Ag or heartworm Ag extracted and purified from male and female worms. These tests are used to screen for feline heartworm disease. The Ab tests have minimal to no cross-reactivity with gastrointestinal (GI) parasitic infections. Ab tests provide greater sensitivity than Ag tests because larvae of either sex can provoke a host immune response. The specificity of the Ab tests for HWD is of some concern, however. Serum Ab to both immature and adult worms is detected as early as 60 days after infection, and some immature heartworm larvae never develop into adults. Therefore a positive Ab test indicates exposure to migrating larvae as well as adults, not the presence of adult heartworms specifically. When the Ab test is positive, other evidence also should be sought to support a diagnosis of HWD. This can include a positive heartworm Ag test or findings consistent with HWD on thoracic radiography and echocardiography. The concentration of Ab does not appear to correlate well with an individual cat's worm burden, nor with the severity

of clinical disease or radiographic signs. High Ab titers are associated with heartworm death as well as heavy infection. It is unclear how long circulating Ab remain after elimination of heartworm infection.

False negative Ab tests also occur fairly frequently (in up to approximately 14% of cases). These are usually related to infection with a single worm and are a matter of concern because the feline worm burden is often low. Therefore a negative heartworm Ab test suggests one of the following: (1) the cat does not have heartworm infection, (2) the cat has an infection less than 60 days old, or (3) the cat produced a concentration of IgG Ab against the Ag used in making the test that is too low to be detected. When clinical findings suggest HWD but the Ab test is negative, serological testing should be repeated using a different Ab test and a heartworm Ag test. Chest radiographs and an echocardiogram are also recommended. The Ab test may also be repeated in a few months.

#### Microfilaria Identification

Tests for circulating microfilariae are no longer recommended for routine heartworm screening. They are useful in identifying patients that are reservoirs of infection and to assess whether high numbers of microfilariae are present before a monthly preventive drug is administered. Microfilaria testing is mandatory if diethylcarbamazine (DEC) is to be used as a heartworm preventive. The macrocyclic lactone preventive drugs, administered monthly, reduce and eliminate microfilaremia by impairing the reproductive function of female and possibly also male worms. Most dogs become amicrofilaremic by the sixth monthly dose with these drugs. However, up to 90% of heartworm-positive dogs that are not treated monthly with a macrolide have circulating microfilariae. The remaining so-called occult infections, in which there are no circulating microfilariae, can result from an immune response that destroys the microfilariae within the lung (true occult infection), unisex infection, sterile adult heartworms, or the presence of only immature worms (prepatent infection). Occult infections are frequently associated with severe signs of disease. Low numbers of microfilariae and diurnal variations in the number of circulating microfilariae in peripheral blood can also cause false-negative microfilaria test results. Circulating microfilariae are rarely found in cats with HWD.

Microfilaria concentration tests that use at least 1 ml of blood are recommended for detecting circulating microfilariae. The nonconcentration tests are more likely to miss low numbers of microfilariae, although they do allow observation of mirofilarial motility. *Dirofilaria* have a stationary rather than a migratory movement pattern. Nonconcentration tests include examination of a fresh wet blood smear or the buffy coat of a spun hematocrit tube.

Concentration tests are done using either a millipore filter or the modified Knott's centrifugation technique. Both techniques lyse the red blood cells and fix any existing microfilariae. The modified Knott test is preferred for measuring larval body size and differentiating *D. immitis* from non-



TABLE 10-1

Morphologic Differentiation of Microfilaria

SMEAR	DIROFILARIA IMMITIS	DIPETALONEMA RECONDITUM
Fresh smear	Few to large numbers	Usually small numbers
	Undulate in one place	Move across field
Stained	Straight body	Curved body
smear*	Straight tail	Posterior extremity hook ("button hook" tail); inconsistent finding
	Tapered head >290 μm long >6 μm wide	Blunt head <275-280 μm long <6 μm wide

<sup>\*</sup>Size criteria given for lysate prepared using 2% formalin (modified Knott's test); microfilariae tend to be smaller with lysate of filter tests. Width and morphology are the best discriminating factors.

pathogenic filarial larvae, such as *Acanthocheilonema* (formerly *Dipetalonema*) *reconditum* (Table 10-1). An occasional false-positive microfilaria test result occurs in animals with microfilariae but no live adult heartworms.

#### HEARTWORM DISEASE IN DOGS

#### Pathophysiology

Heartworm disease is an important cause of pulmonary hypertension (cor pulmonale) in regions where the disease is endemic. Increased pulmonary vascular resistance raises pulmonary arterial pressure according to the relationship: cardiac output =  $\Delta$  pressure/resistance. The presence of adult worms in the pulmonary arteries provokes reactive vascular lesions sthat reduce vascular compliance and lumen size. Within days after young heartworms enter the pulmonary arteries, pathologic changes begin in these vessels. The hostparasite interaction is thought to be more important than the worm number alone in the development of clinical signs, although a large worm burden may be associated with severe disease. The pathogenesis of HWD may be modulated by obligate intracellular bacteria (genus Wolbachia) that are harbored by the worms. This may involve bacterial endotoxins as well as the host immune response to a major Wolbachia surface protein, which is thought to contribute to pulmonary and renal inflammation. Little correlation has been found between pulmonary vascular resistance and the number of worms present. A low worm burden can produce serious lung injury and a greater rise in pulmonary vascular resistance if the cardiac output is high. The increase in pulmonary blood flow associated with exercise exacerbates the pulmonary vascular pathology.

Villous myointimal proliferation of the pulmonary arteries containing heartworms is the characteristic lesion.

The heartworm-induced changes begin with endothelial cell swelling, widening of intercellular junctions, increased endothelial permeability, and periarterial edema. Endothelial sloughing leads to the adhesion of activated white blood cells and platelets. Various trophic factors stimulate smooth muscle cell migration and proliferation within the media and into the intima. Villous proliferations consist of smooth muscle and collagen with an endothelium-like covering. These proliferative changes of the intima occur 3 to 4 weeks after adult worms arrive. They cause luminal narrowing of the smaller pulmonary arteries and also induce further endothelial damage and more proliferative lesions. Hypersensitivity pneumonitis may contribute to parenchymal lung lesions. Endothelial damage promotes thrombosis as well as a perivascular tissue reaction and periarterial edema. Interstitial and alveolar infiltrates may become radiographically apparent; partial lung consolidation develops in some animals. Hypoxic vasoconstriction can also play a role in the vascular changes that increase pulmonary vascular resistance and consequently cause pulmonary hypertension. Dead worms stimulate greater host response and worsen the pulmonary disease. Worm fragments and thrombi cause embolization and a more intense reaction, which eventually leads to fibrosis.

The worm distribution, and accompanying villous proliferation, is most severe in the caudal and accessory lobar arteries. Affected pulmonary arteries lose their normal tapered peripheral branching appearance and appear blunted or pruned. Aneurysmal dilation and peripheral occlusion may occur. The vessels become tortuous and proximally dilated as the increased pulmonary vascular resistance demands higher perfusion pressures.

Right ventricular dilation and concentric hypertrophy are the responses to a chronic requirement for increased systolic pressure. Chronic pulmonary hypertension can lead to right ventricular (RV) myocardial failure, increased RV diastolic pressure, and signs of right-sided congestive heart failure (CHF), especially in conjunction with secondary tricuspid insufficiency. Cardiac output progressively declines as the RV fails. When cardiac output becomes inadequate during exercise, exertional dyspnea, fatigue, and syncope may occur.

Chronic hepatic congestion secondary to HWD may lead to permanent liver damage and cirrhosis. Circulating immune complexes or possibly microfilarial antigens provoke glomerulonephritis. Renal amyloidosis has also been associated with HWD in dogs in rare cases. Occasionally, aberrant worms can cause embolization of the brain, eye, or other systemic arteries.

Although the caudal pulmonary arteries are the preferred site, worm migration to the caudal vena cava is associated with heavy worm burdens. A massive number of worms can cause mechanical occlusion of the RV outflow tract, pulmonary arteries, tricuspid valve region, or venae cavae. This is known as the *caval syndrome*. Cases of systemic arterial migration causing hindlimb lameness, paresthesia, and ischemic necrosis are sporadically described.

## PULMONARY HYPERTENSION WITHOUT HEARTWORM DISEASE

A number of diseases besides HWD are associated with pulmonary hypertension in dogs, including hypoxic pulmonary disease and vascular obstructive disease (e.g., pulmonary thromboembolism). Vascular obstruction reduces total cross-sectional pulmonary vascular area by mechanically obstructing vessels and provoking local hypoxic pulmonary vasoconstriction as well as other reactive changes. Associated pulmonary parenchymal disease can contribute to reduced vascular area.

Chronic elevations in pulmonary venous pressure (as from mitral regurgitation) may increase pulmonary artery pressure but usually only mildly to moderately. Pulmonary edema or congestion associated with high venous pressure can contribute to increased pulmonary vascular resistance by reducing lung compliance and increasing resistance to air flow. Pulmonary overcirculation caused by a congenital cardiac shunt can cause vascular injury and pulmonary arterial remodeling leading to high vascular resistance, pulmonary hypertension and shunt reversal (Eisenmenger's physiology; see p. 109).

#### **Clinical Features**

There is no specific age or breed predilection for HWD in dogs. Although most affected dogs are between 4 and 8 years old, HWD is also diagnosed in dogs <1 year (but >6 months) of age as well as in geriatric animals. Males are affected two to four times as often as females. Large-breed dogs and those living mainly outdoors are at much greater risk of infection than small-breed and indoor dogs. The length of the haircoat does not appear to affect infection risk.

Dogs diagnosed by a positive routine screening test are often asymptomatic. Dogs with occult disease and those not routinely tested are more likely to have advanced pulmonary arterial disease and clinical signs. Dogs with clinical disease often have a history of fatigue, shortness of breath or exertional dyspnea, syncope, cough, hemoptysis, weight loss, or signs of right-sided CHF. A change in or loss of the dog's bark has sometimes been reported.

Physical examination findings may be normal in patients with early or mild disease. Severe disease is frequently associated with poor body condition, tachypnea or dyspnea, jugular vein distention or pulsations, ascites, or other evidence of right-sided CHF. Increased or abnormal lung sounds (wheezes and crackles), a loud and often split second heart sound (S2), an ejection click or murmur at the left heartbase, a murmur of tricuspid insufficiency, or cardiac arrhythmias are variably heard on auscultation. Severe pulmonary arterial disease and thromboembolism can lead to disseminated intravascular coagulation (DIC), thrombocytopenia, epistaxis, and possibly hemoglobinuria. Hemoglobinuria is also associated with caval syndrome. Aberrant worm migration to the central nervous system, eye, femoral arteries, subcutis, peritoneal cavity, and other sites occurs occasionally and causes related signs.

#### **Diagnosis**

#### RADIOGRAPHY

Radiographic findings are often normal early in the disease, although marked changes can develop rapidly in dogs with heavy worm burdens. Characteristic findings include RV enlargement, a pulmonary trunk bulge, and centrally enlarged and tortuous lobar pulmonary arteries with peripheral blunting (Fig. 10-1 and p. 15). The caudal lobar arteries, which are usually the most severely affected, are best evaluated on a dorsoventral (DV) view; the width of these vessels is normally no larger than the ninth rib (at its intersection with the vessels). Enlargement of lobar pulmonary arteries (without concurrent venous distention) is strongly suggestive of HWD or other cause of pulmonary hypertension. An enlarged caudal vena cava also may be seen (see p. 16). Patchy pulmonary interstitial or alveolar infiltrates suggestive of infarction, edema, pneumonia, or fibrosis also are common. These pulmonary opacities may be mainly perivascular. Right-sided CHF caused by HWD is associated with radiographic evidence of severe pulmonary arterial disease and right heart enlargement.

#### **ELECTROCARDIOGRAPHY**

Electrocardiographic (ECG) findings are usually normal, although advanced disease can cause a right axis deviation or an arrhythmia. Dogs with heartworm-induced CHF almost always have ECG criteria for RV enlargement. Tall P waves, suggesting right atrial (RA) enlargement, are sometimes found.

#### **ECHOCARDIOGRAPHY**

Echocardiographic findings in dogs with advanced HWD include RV and RA dilation, RV hypertrophy, paradoxical septal motion, a small left heart, and pulmonary artery dilation. Heartworms located in peripheral pulmonary arteries cannot be seen on echocardiogram. Heartworms within the heart, the main pulmonary artery and its bifurcation, and venae cavae appear as small, bright parallel echos (Fig. 10-2). Suspected caval syndrome can be quickly confirmed by echocardiography. Secondary right-sided CHF may be demonstrated by pleural or pericardial effusion or ascites. Colorflow Doppler can be used in the identification of tricuspid regurgitation even when an audible murmur is absent. Spectral Doppler measurement of maximum tricuspid or pulmonary regurgitant jet velocity allows estimation of pulmonary hypertension severity (see p. 45).

#### CLINICOPATHIC FINDINGS

Eosinophilia, basophilia, and monocytosis are inconsistent hematologic findings. However, fewer than half of dogs with HWD have eosinophilia. Mild regenerative anemia, thought to result from hemolysis, occurs in less than a third of affected dogs. Thrombocytopenia may result from platelet consumption in the pulmonary arterial system, especially after adulticide treatment. DIC also develops in some in dogs with

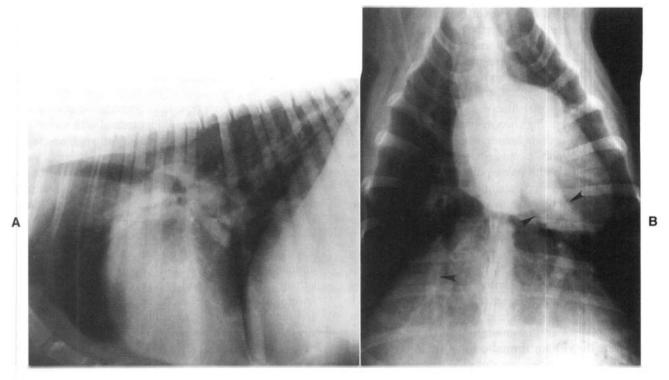


FIG 10-1
Lateral (A) and dorsoventral (B) radiographs from a German Shepherd Dog with advanced heartworm disease. Enlargement of pulmonary arteries is seen, especially on dorsoventral view (arrowheads).

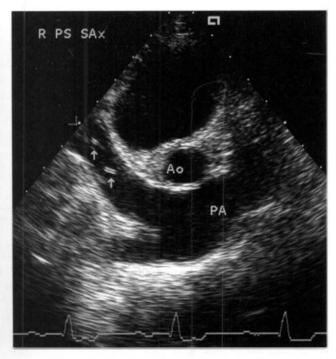


FIG 10-2
Echo image from a dog with severe heartworm disease.
Note the dilated main pulmonary artery (PA) and double-walled echos from heartworms (arrows) in the right PA.
Ao, Aortic root.

advanced disease. The immune response to heartworms produces a polyclonal gammopathy. Mild to moderate elevations in liver enzyme activity and azotemia may occur. Proteinuria is found in 20% to 30% of affected dogs and is more likely with advanced disease. Hypoalbuminemia may develop in severely affected animals.

# Treatment of Dogs with Heartworm Disease PRETREATMENT EVALUATION

As a general rule, adulticide treatment is recommended for dogs infected with heartworms. The withholding of adulticide treatment in some asymptomatic cases remains controversial. Although continuous monthly treatment with prophylactic ivermectin does eventually kill late precardial larvae and young adult worms, this effect occurs over a prolonged time (over 1 to 2 years). Older worms are more resistant to ivermectin and can still cause clinical disease. Furthermore, progression of pulmonary arterial changes, pulmonary disease, and other heartworm-induced effects (e.g., glomerulonephritis) may increase the risk of adulticide treatment should this be undertaken in the future. If adulticide therapy is not given, the dog should at least be treated continuously with ivermectin or possibly with selamectin or moxidectin, which also have some adulticidal effects. Use of heartworm prophylaxis is also important to prevent disease transmission to other animals (by reducing the microfilaremia).

Heartworm-infected dogs should have a thorough history and physical examination. Pretreatment thoracic radiographs provide the best overall assessment of pulmonary arterial and parenchymal disease status. The risk of postadulticide pulmonary thromboembolism is increased in dogs with preexisting clinical and radiographic signs of severe pulmonary vascular disease, especially in those with right-sided CHF or a high worm burden. Other pretreatment tests should include a complete blood count (CBC), serum biochemical profile, and urinalysis. A platelet count is important in animals with severe pulmonary arterial disease. If hypoalbuminemia or proteinuria is detected, a urine protein-creatinine ratio or urine protein loss quantification is advised. Mildly to moderately increased liver enzyme activity may be associated with hepatic congestion, but it does not preclude therapy with melarsomine. Liver enzyme activities usually normalize within 1 to 2 months of heartworm treatment. Some dogs with HWD develop azotemia and/or severe proteinuria. Prerenal azotemia is treated with fluid therapy before adulticide is given. Severe glomerular disease, with loss of antithrombin as well as other proteins, may increase the risk for thromboembolism. Aspirin is not recommended as a routine preadulticide treatment in most dogs because convincing evidence of a beneficial antithrombotic effect is lacking.

The use of prophylactic monthly doses of ivermectin for up to 6 months before the administration of an adulticide in dogs that are clinically stable may be useful. This strategy can reduce heartworm Ag mass by decreasing or eliminating circulating microfilariae and tissue-migrating larvae, stunting immature worm growth, and damaging the adult female reproductive system. Delaying melarsomine for several months also allows any late-stage larvae to mature further, which should increase susceptibility to the adulticidal effect. Microfilaria-positive dogs should be observed in the hospital after the first ivermectin dose in case of adverse reaction. Specific microfilaricide treatment is not necessary before using adulticide.

#### ADULTICIDE THERAPY IN DOGS

Melarsomine dihydrochloride (Immiticide, Merial) is the adulticide of choice. It is effective against both immature and mature heartworms; male worms are more susceptible than females. The worm kill can be controlled by adjusting the dose. An alternative dosing protocol is advised for dogs with more severe disease to promote a more gradual worm kill.

Melarsomine is rapidly absorbed from the intramuscular (IM) injection site. Unchanged drug and a major metabolite are rapidly eliminated in the feces; a minor metabolite is excreted in urine. The drug should be given by deep IM injection into the epaxial lumbar muscles (L3 to L5 region), exactly as recommended by the manufacturer. The lumbar muscle site provides good vascularity and lymphatic drainage with minimal fascial planes. Furthermore, gravity may help prevent the drug from leaking into subcutaneous tissues, where it can cause more irritation. The drug does cause a local reaction at the injection site; this is clinically noticeable

in about a third of treated dogs. Melarsomine is available as a sterile lyophilized powder in 50-mg vials. The rehydrated product is fully stable for 24 hours if kept refrigerated in the dark.

Coughing or gagging and (less often) dyspnea after treatment may be related to the HWD itself, although pulmonary congestion is reported as a toxic effect of overdosing. Most clinical signs noted in dogs treated with melarsomine have been behavioral (e.g., tremors, lethargy, unsteadiness and ataxia, restlessness), respiratory (e.g., panting, shallow breathing, labored respirations, crackles), or injection-site related (e.g., edema, redness, tenderness, vocalization, increased aspartate aminotransferase and creatine kinase activities). Injection site reactions are generally mild to moderate and resolve within 4 (to 12) weeks. Occasionally these reactions are severe. The manufacturer reports that firm nodules may persist indefinitely at the sites. General signs of lethargy, depression, and anorexia occur in about 15% or fewer dogs; other adverse effects, including fever, vomiting, and diarrhea, occur occasionally. Adverse effects are generally mild at recommended doses. Hepatic and renal changes have not proved clinically relevant in animals receiving recommended doses of melarsomine. Overall melarsomine causes less systemic toxicity than its predecessor, thiacetarsamide. Nevertheless, melarsomine has a low margin of safety. Overdose may cause collapse, severe salivation, vomiting, respiratory distress resulting from pulmonary inflammation and edema, stupor, and death. Some clinical reversal of melarsomine toxicity may be achieved with BAL (British Anti-Lewisite or dimercaprol) at a dose of 3 mg/kg, administered intramuscularly. This also decreases adulticide activity.

The HWD severity is used to guide melarsomine therapy (Table 10-2). Standard therapy is used for dogs with mild (class 1) to moderate (class 2) disease. Standard therapy (Box 10-1) involves two doses of 2.5 mg/kg given intramuscularly, 24 hours apart. The manufacturer's administration instructions should be followed carefully. Dogs with severe disease (class 3) or those in class 2 in which a more conservative approach is desired are treated with the alternative dosing regimen. This is designed to partially reduce the worm burden with an initial injection, followed by the standard adulticide regimen 1 month later. The risk of massive pulmonary thromboembolism and death resulting from an initially heavy worm kill is reduced with this protocol. Dogs with caval syndrome (class 4) should not be given adulticide treatment until worms are surgically removed (see p. 177).

Strict rest should be enforced for 4 to 6 weeks after adulticide therapy to reduce the effects of adult worm death and pulmonary thromboembolism (see p. 176). The rest period for working dogs should probably be longer because increased pulmonary blood flow in response to exercise exacerbates pulmonary capillary bed damage and subsequent fibrosis.

Heartworm Ag testing is recommended 6 months after adulticide treatment; results should be negative with successful treatment. Many dogs are heartworm Ag-negative by 4 months after adulticide therapy. Incomplete worm kill is associated with persistent antigenemia. The decision to



**TABLE 10-2** 

#### Classification of Heartworm Disease Severity in Dogs

CLASS	CLINICAL SIGNS	RADIOGRAPHIC SIGNS	LABORATORY ABNORMALITIES
1 (mild)	None; or occasional cough, fatigue on exercise, or mild loss of condition	None	None
2 (moderate)	None; or occasional cough, fatigue on exercise, or mild to moderate loss of condition	Right ventricular enlargement and/or some pulmonary artery enlargement; ±perivascular and mixed alveolar/interstitial opacities	±Mild anemia (PCV to 30%); ±proteinuria (2+ on dipstick)
3 (severe)	General loss of condition or cachexia; fatigue on exercise or mild activity; occasional or persistent cough; ±dyspnea; ±right-sided heart failure	Right ventricular ± atrial enlargement; moderate to severe pulmonary artery enlargement; perivascular or diffuse mixed alveolar/interstitial opacities; ±evidence of thromboembolism	Anemia (PCV < 30%); proteinuria (≥2+ on dipstick)
4 (very severe) Caval syndrome	See p. 177		

PCV, Packed cell volume.



#### BOX 10-1

#### Checklist for Melarsomine (Immiticide) Adulticide Therapy in Dogs

#### Before starting treatment

- 1. Confirm diagnosis.
- 2. Conduct pretreatment evaluation and management.
- 3. Determine class (severity) of disease (see Table 10-2).
- 4. Determine melarsomine (Immiticide) treatment protocol.\* Standard treatment protocol (for class 1 and many class 2 dogs)
- Reconstitute melarsomine as directed by manufacturer. (Use immediately or within 24 hours if refrigerated and protected from light.)
- Draw 2.5 mg/kg of Immiticide into a syringe; attach a new, sterile needle: 23-gauge, 1-inch (2.5-cm) long for dogs <10 kg; or 22-gauge, 1.5-inch (3.75-cm) long for dogs >10 kg.
- Give by deep intramuscular injection into lumbar (epaxial) musculature in the L3 to L5 region; avoid subcutaneous leakage. Record location of first injection.

- 4. Repeat steps 1 to 3 at 24 hours after first dose; use opposite side for second injection.
- Enforce rest for 4 to 6 weeks minimum; symptomatic treatment as needed.

Alternate treatment protocol (for class 3 and some class 2 dogs)

- 1. Provide symptomatic treatment as needed; enforce rest.
- When condition is stable, administer one dose of 2.5 mg/kg as described in the standard treatment protocol.
- Continue enforced rest and symptomatic treatment as needed.
- Between 4 and 6 weeks later, administer two more doses,
   hours apart, according to the standard treatment protocol.

repeat adulticide therapy is guided by the patient's overall health, performance expectations, and age. Complete worm kill is probably not necessary; even if some adult heartworms survive, pulmonary arterial disease improves considerably after adulticide therapy.

Thiacetarsamide is an older adulticide agent that may still be available. It has no advantages and several disadvantages compared with melarsomine. Likewise, the use of other drugs, such as levamisole or stibophen, as adulticides is not recommended. Levamisole does not consistently kill adult heartworms, although it is somewhat effective against male worms and may sterilize adult female worms.

# Postadulticide Pulmonary Thromboembolic Complications

Pulmonary arterial disease worsens from 5 to 30 days after adulticide therapy and is especially severe in previously symptomatic dogs. It occurs because dead and dying worms lead to thrombosis and pulmonary artery obstruction, with exacerbation of platelet adhesion, myointimal proliferation,

<sup>\*</sup>See p. 174 for more information.

villous hypertrophy, granulomatous arteritis, perivascular edema, and hemorrhage. Pulmonary blood flow obstruction and increased vascular resistance further strain the right ventricle and increase oxygen demand. Poor cardiac output, hypotension, and myocardial ischemia may result. Severe ventilation-perfusion mismatch may result from pulmonary hypoperfusion, hypoxic vasoconstriction and bronchoconstriction, pulmonary inflammation, and fluid accumulation. Pulmonary thromboembolization is most likely to occur 7 to 17 days after adulticide therapy. As expected, the caudal and accessory lung lobes are most commonly and severely affected.

Depression, fever, tachycardia, tachypnea or dyspnea, and cough are common clinical signs. Hemoptysis, right-sided CHF, collapse, or death may also occur. Interstitial and alveolar pulmonary inflammation and fluid accumulation cause pulmonary crackles on auscultation. Focal lung consolidation may cause areas of muffled lung sounds. Thoracic radiographs show patchy alveolar infiltrates with air bronchograms, especially near the caudal lobar arteries. Thrombocytopenia or neutrophilia with a left shift may be seen on CBC.

Treatment of pulmonary thromboembolism includes strict rest (i.e., cage confinement) and glucocorticoid therapy to reduce pulmonary inflammation (prednisone, 1 to 2 mg/ kg/day by mouth initially, then tapering). Supplemental oxygen therapy is recommended to reduce hypoxiamediated pulmonary vasoconstriction. A bronchodilator (e.g., oral aminophylline, 10 mg/kg IM or IV q8h; or oral theophylline, 9 mg/kg q6-8h), judicious fluid therapy (if there is evidence of cardiovascular shock), and cough suppressants may be useful. Antibiotics have been given empirically, but they are of questionable benefit unless there is evidence of concurrent bacterial infection. Hydralazine has reduced pulmonary vascular resistance experimentally, and some dogs seem to respond clinically to diltiazem. Systemic hypotension and tachycardia must be avoided when using a vasodilator. Aspirin is not recommended because there is no convincing evidence that it prevents thrombosis or reduces pulmonary arteritis. Heparin (200 to 400 U/kg sodium heparin administered subcutaneously q8h, or 50 to 100 U/kg calcium heparin administered subcutaneously q8-12h) may be considered for severe cases of thromboembolism. However, excessive bleeding is a possible serious adverse effect. Low-molecular-weight heparin might provide a safer alternative to unfractionated heparin, but definitive recommendations are not yet available.

Endothelial changes in survivors regress within 4 to 6 weeks. Pulmonary hypertension and arterial disease, along with radiographic changes, diminish over the next several months. Eventually, pulmonary arterial pressure and the contour of the proximal pulmonary arteries normalize, although some fibrosis may remain.

#### Treatment of Dogs with Complicated HWD

#### **PULMONARY COMPLICATIONS**

Immune-mediated pneumonitis occurs in some dogs. Allergic or eosinophilic pneumonitis develops in a minority of

dogs with occult HWD. Clinical manifestations of heartworm pneumonitis include a progressively worsening cough, crackles heard on auscultation, tachypnea or dyspnea, and sometimes cyanosis, weight loss, and anorexia. Eosinophilia, basophilia, and hyperglobulinemia are inconsistent findings. Heartworm Ag tests are usually positive. Diffuse interstitial and alveolar infiltrates, especially in the caudal lobes, are common on radiographs; these can be similar to those in dogs with pulmonary edema or blastomycosis. There is often no clinically relevant cardiomegaly or pulmonary lobar artery enlargement. Tracheal wash cytology usually reveals a sterile eosinophilic exudate with variable numbers of well-preserved neutrophils and macrophages. Therapy with a glucocorticoid (prednisone, 1-2 mg/kg/day by mouth initially) usually results in rapid and marked improvement. Prednisone may be continued as needed, in gradually tapered doses (to 0.5 mg/kg every other day) and does not appear to adversely affect the adulticide efficacy of melarsomine.

Pulmonary eosinophilic granulomatosis is an uncommon syndrome that has been associated with HWD, although some affected dogs have negative heartworm tests. Its pathogenesis is thought to involve a hypersensitivity reaction to heartworm Ag or immune complexes, or both. Pulmonary granulomas comprise a mixed mononuclear and neutrophilic cell population, with many eosinophils and macrophages. A proliferation of bronchial smooth muscle within granulomas and an abundance of alveolar cells in the surrounding area are common findings. Lymphocytic and eosinophilic perivascular infiltrates may also occur. Eosinophilic granulomas involving the lymph nodes, trachea, tonsils, spleen, GI tract, and the liver or kidneys may occur concurrently. The clinical signs of pulmonary eosinophilic granulomatosis are similar to those of eosinophilic pneumonitis. Clinicopathologic findings variably include leukocytosis, neutrophilia, eosinophilia, basophilia, monocytosis, and hyperglobulinemia. In some cases an exudative, primarily eosinophilic pleural effusion develops. Radiographic findings include multiple pulmonary nodules of varying size and location with mixed alveolar and interstitial pulmonary infiltrates; hilar and mediastinal lymphadenopathy may also be present. Eosinophilic granulomatosis is treated initially with prednisone (1 to 2 mg/kg q12h); however, additional cytotoxic therapy may be needed as well. Not all dogs respond completely, and relapses are common, especially when therapy is reduced or discontinued. The response to immunosuppressive drugs after relapse may be poor. Therapy for adult heartworms is given when pulmonary disease improves.

Severe pulmonary arterial disease is more common in dogs with long-standing heartworm infection, in those with many adult worms, and in active dogs. Severe cough, exercise intolerance, tachypnea or dyspnea, episodic weakness, syncope, weight loss, and ascites are common clinical signs; death sometimes occurs. Typical radiographic findings include markedly enlarged, tortuous, and blunted pulmonary arteries. Pulmonary parenchymal infiltrates leading to hypoxemia are seen in some cases; these are treated with prednisone as described in the preceding paragraph. Throm-

bocytopenia and hemolysis may occur in dogs with severe pulmonary arterial disease and thromboembolism. Monitoring of platelet count and packed cell volume is recommended. DIC develops in some dogs. Conservative therapy with oxygen, prednisone, and a bronchodilator (e.g., theophylline), as for postadulticide pulmonary thromboembolism, should help improve oxygenation and reduce pulmonary artery pressures. Alternate-day, low-dose prednisone (e.g., 0.5 mg/kg orally) is thought to have beneficial antiinflammatory effects, although long-term use of high corticosteroid doses may reduce pulmonary blood flow, increase risk of thromboembolism, and inhibit vascular disease resolution.

After the animal's condition is stabilized, the alternative melarsomine protocol may be used. Use of aspirin is discouraged, especially with hemoptysis. Prophylactic antibiotics are sometimes recommended because of the potential for secondary bacterial infections in devitalized pulmonary tissue.

## RIGHT-SIDED CONGESTIVE HEART FAILURE

Severe pulmonary arterial disease and pulmonary hypertension can cause CHF. Jugular venous distention or pulsation, ascites, syncope, exercise intolerance, and arrhythmias are typical signs. Pleural or pericardial effusion as well as other signs secondary to pulmonary arterial and parenchymal disease may also occur. Treatment is the same as for dogs with severe pulmonary arterial disease, with the addition of furosemide (e.g., 1-2 mg/kg/day), an angiotensin-converting enzyme inhibitor (ACEI; e.g., enalapril 0.5 mg/kg q12-24 h by mouth), and a sodium-restricted diet. Use of digoxin in these cases is controversial; pimobendan has not been evaluated in this setting but could be useful.

#### CAVAL SYNDROME

The (vena) caval syndrome occurs in heavily infected animals when venous inflow to the heart is obstructed by a mass of worms, leading to low-output cardiovascular shock. Other terms for this condition include postcaval syndrome, acute hepatic syndrome, liver failure syndrome, dirofilarial hemoglobinuria, and vena cava embolism. As the heartworm burden increases, adult worms migrate to the right atrium and caudal vena cava from their preferred locations in the pulmonary artery and right ventricle. Factors other than worm burden alone are probably also involved in the development of the caval syndrome, including degree of pulmonary hypertension. Caval syndrome occurs more often in geographic areas where HWD is enzootic; up to 20% of dogs with HWD are estimated to be affected in some areas.

Most dogs that develop caval syndrome have no history of heartworm-related signs. Acute collapse is common, often accompanied by anorexia, weakness, tachypnea or dyspnea, pallor, hemoglobinuria, and bilirubinuria. A tricuspid insufficiency murmur, jugular distention and pulsations, weak pulses, a loud and possibly split S<sub>2</sub>, and a cardiac gallop rhythm are often found. Sometimes coughing or hemoptysis and ascites occur. Tricuspid insufficiency and partial occlusion of RV inflow caused by a mass of worms, in conjunction

with pulmonary hypertension, lead to the development of right-sided congestive signs and poor cardiac output.

Clinicopathologic findings may include microfilaremia, Coombs-negative fragmentation hemolytic anemia (from red blood cell trauma), azotemia, abnormal liver function, and increased liver enzyme activities; DIC is common. Intravascular hemolysis results in hemoglobinemia and hemoglobinuria. Thoracic radiographs indicate right heart and pulmonary artery enlargement. The ECG usually suggests RV enlargement. Ventricular or supraventricular premature complexes are common. Echocardiography reveals a mass of worms entangled at the tricuspid valve and in the right atrium and venae cavae (Fig. 10-3). RV dilation and hypertrophy, paradoxical septal motion, and a small left ventricle are also typical.

Most dogs die within 24 and 72 hours as a result of cardiogenic shock complicated by metabolic acidosis, DIC, and anemia unless they are aggressively treated. Worms must be surgically removed from the vena cava and right atrium as soon as possible. The dog is lightly sedated, if necessary, and local anesthesia is used. A right jugular venotomy with the dog restrained in left lateral recumbency is the usual approach. Long alligator forceps, an endoscopic basket retrieval instrument, or horsehair brush device are used to grasp and withdraw the heartworms through the jugular vein incision. The instrument is gently passed down the vein into the right atrium; repositioning of the animal's head and neck may be necessary to pass the instrument beyond the thoracic inlet. The goal is to retrieve as many worms as possible; generally, five to six unsuccessful attempts in sequence is the end point. Resistance to instrument withdrawal from the vein may occur if too many worms are grasped at once or a cardiovascular structure is grabbed by forceps. Survival rates of 50% to 80% have been reported for dogs undergoing this procedure. Another technique that has been used in very small dogs is right auricular cannulation performed via a thoracotomy to remove worms. (See Suggested Readings for more information on this technique.)

Cautious intravenous (IV) fluid administration with other supportive care is provided during and after surgical worm removal. Central venous pressure monitoring helps the clinician assess the effectiveness of worm removal and fluid therapy. Treatment with a positive inotrope or sodium bicarbonate is usually not necessary, but a broad spectrum antibiotic is recommended. Monitoring for anemia, thrombocytopenia, DIC, and organ dysfunction is important; treatment is given as indicated. Severe pulmonary thromboembolism and renal or hepatic failure are associated with poor outcome. Dogs that survive acute caval syndrome can be treated with adulticide within a few weeks after stabilization to eliminate remaining worms. The use of a flexible alligator forceps with fluoroscopic or transesophageal echo guidance has been advocated as a way to reduce the worm burden in the main pulmonary artery and lobar branches before adulticide therapy. This can reduce the risk for postadulticide thromboembolism in heavily infected dogs, although technical issues and the need for heavy sedation or anesthesia may be limitations.

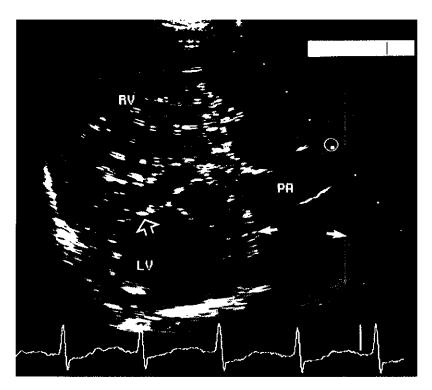


FIG 10-3

Echocardiogram from a 9-year-old male mixed-breed dog with caval syndrome. The transducer is in the right parasternal short-axis position at a level just below the aorta. The image shows the enlarged and hypertrophied right ventricle and its outflow tract. Many small, bright parallel echoes are apparent in the body of the right ventricle (RV) in this diastolic frame and are caused by a clump of heartworms entangled in the tricuspid valve apparatus. Note also the widened main pulmonary artery segment typical of pulmonary hypertension (small arrows). The interventricular septum is flattened and pushed toward the left ventricle (LV) by high right ventricular pressure (open arrow). The LV itself is small because the heartworms obstruct blood flow through the right heart. PA, Main pulmonary artery.

#### MICROFILARICIDE THERAPY

Specific microfilaricidal therapy for dogs with circulating microfilariae may be given 3 to 4 weeks after adulticide therapy, but the gradual microfilaricidal effect of monthly preventive drugs has largely replaced the need for this treatment. Oral ivermectin (at 50 µg/kg) and milbemycin oxime (at standard preventive dose) can rapidly reduce microfilariae. Ivermectin at this dose is safe for Collies. The rapid death of many microfilariae can cause systemic effects within 3 to 8 (and occasionally 12) hours of the first dose; these include lethargy, inappetence, excessive salivation, retching, defecation, pallor, and tachycardia. Such adverse effects are usually mild, but dogs with a high number of circulating microfilariae may experience circulatory collapse. This condition generally responds to glucocorticoid therapy (e.g., prednisolone sodium succinate, 10 mg/kg, or dexamethasone, 1 mg/kg, administered intravenously) and IV fluid administration (e.g., 80 ml/kg over 2 hours) if these are instituted promptly. All cases should be closely observed for 8 to 12 hours after initial microfilaria treatment with either macrolide. An additional benefit is protection against new infection. Moxidectin and selamectin are also known to be microfilaricidal, but clinical experience for this purpose is lacking. Other drugs used as microfilaricides in the past (e.g., levamisole and fenthion) are not recommended because of lower efficacy and frequent adverse effects.

#### **HEARTWORM PREVENTION**

Heartworm prophylaxis is indicated for all dogs living in endemic areas. The time of year that infection can occur is limited in many geographic areas, because sustained warm, moist conditions are needed for transmission of the disease. Transmission can occur only during a few months in the most northern parts of the United States and Canada; year-round transmission is likely only in the far south of the continental United States. Although monthly preventive therapy may be necessary only during June through November in most of the United States, continuous chemoprophylaxis throughout the year may be more practical in locations where transmission is likely during more than half the year.

Several drugs are currently available for preventing heartworm disease: the avermectins (ivermectin, selamectin) and the milbemycins (milbemycin oxime, moxidectin). Diethycarbamazine (DEC) is another choice, but it must be given daily. The avermectins and milbemycins induce neuromuscular paralysis and death in nematode (and arthropod) parasites by interacting with membrane chloride channels. They are effective against third- and fourth-stage larvae and sometimes young adult worms as well as microfilariae; however, milbemycin is least effective against adult *D. immitis*. Retroactive efficacy (reachback) with these agents lasts at least 1 and possible more than 2 months after a single dose. These agents are quite safe in mammals when used as directed, even in sensitive Collies. Cases of clinical toxicity have usually been related to dosage miscalculation using a concentrated livestock preparation.

The avermectins and milbemycins are packaged in monthly dose units according to body weight ranges. Dosing should begin within 1 month of the start of the heartworm transmission season and continue to within 1 month after the transmission season ends. Year-round administration may be preferable depending on location. Drugs available for monthly oral administration include ivermectin (6-12 µg/ kg; Heartgard, Merial), milbemycin oxime (0.5-1.0 mg/kg; Interceptor, Novartis Animal Health), and moxidectin (3 µg/ kg; ProHeart, Fort Dodge Animal Health). Selamectin (Revolution, Pfizer Animal Health) is applied to the skin between the shoulder blades at a monthly dose range of 6-12 mg/kg; efficacy is not affected if bathing or swimming is delayed at least 2 hours after application. Some of these agents are effective against other parasites at the doses used for heartworm prevention (e.g., hookworms with milbemycin; fleas, earmites, and ticks with selamectin). These drugs are also sometimes marketed in combination with other antiparasitic agents for broader protection against endoparasites and ectoparastites.

DEC (at 3 mg/kg, or 6.6 mg/kg of the 50% citrate, by mouth once daily) has been used for decades to prevent HWD. The drug is thought to affect the heartworm's L<sub>3</sub> to L<sub>4</sub> molting stage at 9 to 12 days after infection. The drug may be discontinued 2 months after a killing frost in regions with cold winters and reinstituted 1 month before mosquito season in the spring. Before beginning (or restarting) DEC treatment, dogs must be negative for microfilariae (see p. 170). Puppies 6 months of age and older also should be tested for microfilariae. Annual microfilaria tests are strongly recommended, even in areas where the drug is given yearround. To be effective, DEC must be given daily. If a lapse in DEC administration of <6 weeks has occurred, one dose of a monthly preventive drug should restore protection. For longer lapses, monthly chemoprophylaxis should be extended for a year. Microfilaria-positive dogs should not be given DEC. Adverse reactions of variable severity may occur, especially in dogs with higher numbers of microfilariae. These may include lethargy progressing to vomiting, diarrhea, and bradycardia; some patients develop hypovolemic shock, with tachypnea, tachycardia, recumbency, hypersalivation, and eventually death. IV dexamethasone (at least 2 mg/kg), fluids, and other supportive measures have been used to treat the hypovolemia and shock; atropine is used for severe bradycardia. Dogs with this microfilaria-induced reaction that do not show clinical improvement within 3 to 5 hours are likely to die. Dogs without circulating microfilariae may be given DEC. Those on DEC prophylaxis that are subsequently discovered to have circulating microfilariae may be continued on the drug without interruption during adulticide and microfilaricide therapy to prevent reinfection.

Preventive therapy can begin at 6 to 8 weeks of age. Dogs old enough to have been previously infected should be tested for circulating Ag and (if DEC is to be used) microfilariae before chemoprophylaxis is initially begun. Retesting for heartworm Ag every 2 to 3 years is probably adequate when monthly preventive agents are used. When DEC is chosen as a preventive, yearly microfilaria testing is important before DEC is reinstituted.

#### **HEARTWORM DISEASE IN CATS**

#### **Pathophysiology**

In cats the pathophysiologic changes associated with HWD occur in two stages. Approximately 3 to 6 months after infection, immature worms arrive, and may die, in the pulmonary arteries. This stimulates pulmonary intravascular macrophage activation. These specialized phagocytic cells are located in the pulmonary capillary beds of cats but not dogs. Activation of these macrophages leads to acute inflammation in the pulmonary arteries and lung tissue. Adventitial and perivascular inflammatory cell infiltrates of eosinophils and neutrophils are seen as well. Cats also have more extensive alveolar type 2 (surfactant-producing) cell hyperplasia than dogs, which can interfere with alveolar O2 exchange. The parenchymal lesions are thought to play an important role in the development of acute respiratory distress in cats 3 to 9 months after infection. The acronym HARD (heartworm-associated respiratory disease) has been proposed for the lesions and subsequent clinical signs that may result from the death of L<sub>5</sub> larvae in the lungs of these cats. Although some cats recover, this phase is fatal in others. Sudden death can occur.

In cats that survive, the acute inflammation subsides. Vascular injury leads to myointimal proliferations and muscular hypertrophy in affected pulmonary arteries. These lesions tend to be focal. This may be why clinically relevant pulmonary hypertension, secondary RV hypertrophy, and right-sided CHF are uncommon in cats. Dead and degenerating worms cause recrudescence of pulmonary inflammation and thromboembolism. Disease is most severe in the caudal lung lobes. Caudal lobar arterial obstruction can be caused by villous proliferation, thrombi, or dead heartworms. Adult worms are more likely to obstruct the pulmonary arteries of cats (compared with dogs) by virtue of their relative size. The bronchopulmonary circulation in cats is thought to prevent pulmonary infarction.

Vomiting is common in cats with HWD. The mechanism for this may involve central stimulation (of the chemoreceptor trigger zone) by inflammatory mediators. Antiinflammatory doses of a glucocorticoid often control this sign. Infected cats generally have fewer adult worms than do infected dogs. Heartworms mature more slowly, fewer numbers of infective larvae mature to adults, and the adult life span is shorter in cats. However, live worms can persist for 2 to 3 years. Heartworm-infected cats generally have fewer than eight adult worms in the RV and pulmonary arteries, and most cats have only one or two worms. Nevertheless, even one adult worm can cause death. Unisex infection is common. Most cats have no or only a brief period of microfilaremia. Aberrant worm migration is also more common in cats than dogs and complicates necropsy confirmation of infection. Aberrant sites have included the brain, subcutaneous nodules, body cavities, and occasionally a systemic artery.

#### **Clinical Features**

Most reported cases have occurred in cats 3 to 6 years of age, although cats of any age are susceptible. Domestic Shorthair cats seem to be overrepresented. Male cats are overrepresented in some but not all studies. Cats living strictly indoors are not protected from infection. Infection is self-limiting in some cats. Some researchers have noted an increase in HWD diagnosis during fall and winter, presumably after infection in the spring, but others have found fewer cases in the latter part of the year.

Clinical signs are variable and may be transient or nonspecific. Respiratory signs occur in more than half of symptomatic cats, especially dyspnea and/or paroxysmal cough, which can mimic feline asthma. Other client complaints include lethargy, anorexia, vomiting, syncope, other neurological signs, and sudden death. Vomiting, usually unrelated to eating, is common and may be the only sign in some infected cats. Severe clinical signs are usually associated with the arrival of L<sub>5</sub> worms in the pulmonary arteries (and HARD surrounding the death of some L<sub>5</sub>) and also with thromboembolism after the death of one or more adult worms. The sudden onset of neurologic signs, with or without anorexia and lethargy, is common during aberrant worm migration. Such signs include seizures, dementia, apparent blindness, ataxia, circling, mydriasis, and hypersalivation. Only rarely do cardiopulmonary and neurologic signs co-exist. Although heartworms can cause significant pulmonary disease, some cats have no clinical signs.

Auscultation may reveal pulmonary crackles, muffled lung sounds (either from pulmonary consolidation or pleural effusion), tachycardia, and sometimes a cardiac gallop sound or murmur. Pleural effusion caused by right-sided CHF, as well as syncope, is less common in cats than in dogs with HWD. However, chylothorax and ascites are occasionally associated with HWD in cats, and pneumothorax occurs rarely. There are sporadic reports of caval syndrome in cats.

Peracute respiratory distress, ataxia, collapse, seizures, hemoptysis, or sudden death may occur.

#### **Diagnosis**

Definitive diagnosis is more difficult in cats than dogs. A combination of serologic testing (see p. 170), thoracic radio-

graphs, and echocardiography is used. Microfilaria testing is only occasionally helpful.

#### TESTS FOR HEATWORM DISEASE IN CATS Serologic Tests

Feline heartworm Ab tests are often used for screening; however, although they are fairly sensitive, they are not specific for adult heartworms. The ELISA-based Ag tests are highly specific in detecting adult heartworm infection, but their sensitivity depends on the gender, age, and number of worms. Serologic test results may be negative early in the infection, although the cat may have clinical signs. Ag test results are negative during the first 5 months after infection and may be variably positive at 6 to 7 months; infections with mature female worms should be detected after 7 months. False-negative heartworm Ag test results are more likely in cats because worm burden is typically low; also, a longer time is required for cats to become Ag positive. Acute death and severe clinical signs may occur in Ag-negative cats. Furthermore, postmortem diagnosis may be difficult if the worms are located in distal pulmonary arteries or aberrant sites. Occasionally, a positive Ag test result occurs but no worms are found on postmortem examination. Spontaneous worm death, worms overlooked during pulmonary evaluation, and ectopic infection are likely reasons for this finding.

#### **RADIOGRAPHY**

Radiographic findings that suggest HWD include pulmonary artery enlargement with or without visible tortuosity and pruning, RV or generalized cardiac enlargement, and diffuse or focal pulmonary bronchointerstitial infiltrates (Fig. 10-4). Pulmonary hyperinflation is sometimes evident. The pulmonary artery and right heart changes are typically more subtle in cats than dogs. Radiographic findings may not correlate with clinical signs or results of serologic tests. Pulmonary artery distention may be greatest within the first 7 months of infection; some regression may occur subsequently, especially in cranial arteries. The DV view is best for evaluating caudal lobar arteries; these are more frequently abnormal on radiographs. The right caudal lobar artery may be more prominent; however, a left caudal pulmonary artery ≥1.6 multiplied by the width of the ninth rib at the ninth intercostal space was reported as the most discriminating radiographic finding for separating heartworm-infected from non-infected cats (Schafer et al., 1995). The main pulmonary artery segment is not usually visible on DV or ventrodorsal views in cats because its location is more medial than it is in dogs. Marked right heart enlargement is more likely when signs of right-sided CHF (e.g., pleural effusion) exist. Thoracocentesis may be necessary to evaluate the heart, pulmonary vasculature, and lung parenchyma when there is pleural effusion. Ascites occurs in some cats with HWD, but it is rare in cats with heart failure resulting from cardiomyopathy.

Both heartworm-associated pneumonitis as well as pulmonary thromboembolism produce pulmonary infiltrates;

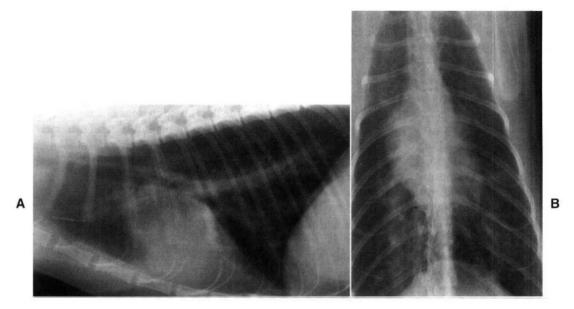


FIG 10-4
Lateral (A) and dorsoventral (B) radiographs from a cat with heartworm disease. There are interstitial infiltrates throughout the lung fields and enlarged pulmonary arteries seen on both views.

focal perivascular and interstitial opacities are more common than diffuse infiltrates. Radiographs are normal in a small minority of heartworm-infected cats.

Pulmonary arteriography may confirm a suspected diagnosis of HWD in a cat with a false-negative Ag test result and normal echocardiogram. The study may be performed using a large-bore jugular catheter. Morphologic changes in the pulmonary arteries are outlined, and worms appear as linear filling defects.

#### **ECHOCARDIOGRAPHY**

Echocardiographic findings may be normal unless worms are located in the heart, main pulmonary artery segment, or proximal left and right pulmonary arteries. However, heartworms may be visualized in about one half to three fourths of infected cats. Higher numbers of worms increase the likelihood of identification with echocardiography. Because worms are seen more often in the pulmonary arteries than in right heart chambers, an index of suspicion and careful interrogation of these structures are important.

#### **ELECTROCARDIOGRAPHY**

ECG findings are often normal, but most cats with heart-worm-induced CHF have changes suggesting RV enlargement. Arrhythmias appear to be uncommon. Advanced pulmonary arterial disease and CHF are more likely to cause ventricular tachyarrhythmias.

#### OTHER TESTS

Between one and two thirds of infected cats have peripheral eosinophilia, usually from 4 to 7 months after infection. Many times the eosinophil count is normal; basophilia is uncommon. About one third of the cases have mild nonre-

generative anemia. Advanced pulmonary arterial disease and thromboembolism may be accompanied by neutrophilia (sometimes with a left-shift), monocytosis, thrombocytopenia, and DIC. Hyperglobulinemia, the most common biochemical abnormality, occurs inconsistently. The prevalence of glomerulopathies in cats with HWD is unknown, but it does not appear to be high.

Tracheal wash or bronchoalveolar lavage specimens may show an eosinophilic exudate that suggests allergic or parasitic disease, similar to that found with feline asthma or pulmonary parasites. This finding usually occurs between 4 and 8 months after infection. Later in the disease, tracheal wash findings may be unremarkable or indicate nonspecific chronic inflammation. Pleural effusion resulting from heartworm-induced CHF is generally a modified transudate, although chylothorax occasionally develops.

At around 6.5 to 7 months after infection, a transient (1 to 2 months in duration), low-grade microfilaremia occurs in about half of infected cats. Therefore microfilaria concentration tests are usually negative. Nevertheless, a concentration test may still prove valuable in some individual cats. Between 3 and 5 ml, rather than 1 ml, of blood should be used to increase the probability of detecting microfilariae.

#### Treatment of Cats with Heartworm Disease

# MEDICAL THERAPY AND COMPLICATIONS

Adulticide therapy is not recommended in most cases because the likelihood of severe complications in this species is high. Also, spontaneous cure is possible in cats because of the shorter heartworm life span, and cats are not significant reservoirs for HWD transmission to other animals. On the basis of a retrospective study (Atkins et al., 2000), cats treated with thiacetarsamide had no survival advantage over those that were not treated with adulticide.

The recommended, and more conservative, approach for infected cats is to use prednisone as needed for respiratory signs and radiographically evident pulmonary interstitial infiltrates. A monthly heartworm preventive drug is also advised but not a heartworm adulticide. Serologic tests (for heartworm Ab and Ag) are obtained every 6 to 12 months to monitor infection status. Ag-positive cats usually become negative within 4 to 5 months of worm death. It is unclear how long Ab tests remain positive. Serial thoracic radiographs and echocardiograms also can be useful for monitoring cats that have had abnormal findings. Interstitial pulmonary infiltrates usually respond to prednisone (e.g., 2 mg/kg/day by mouth, reduced gradually over 2 weeks to 0.5 mg/kg god, then discontinued after 2 more weeks). Prednisone therapy may be repeated periodically if respiratory signs recur.

The possibility of severe respiratory distress and death is always present, especially after spontaneous or adulticideinduced worm death. Pulmonary thromboembolism is more likely to produce a fatal outcome in cats than dogs. Clinical findings with pulmonary thromboembolism include fever, cough, dyspnea, hemoptysis, pallor, pulmonary crackles, tachycardia, and hypotension. Radiographic signs include poorly defined, rounded or wedge-shaped interstitial opacities that obscure associated pulmonary vessels. Alveolar infiltrates are seen in some cases. Cats with acute disease are given supportive care, which may include an IV glucocorticoid (e.g., 100 to 250 mg prednisone sodium succinate), fluid therapy, a bronchodilator, and supplemen-tal oxygen. Diuretics are not indicated. Aspirin is currently not recommended for cats with HWD. Aspirin and other nonsteroidal antiinflammatory drugs have not been shown to produce benefit and may exacerbate pulmonary disease.

Right-sided CHF develops in some cats with severe pulmonary arterial disease. Cough and other signs of pulmonary interstitial disease or a thromboembolic event occur inconsistently. Dyspnea (caused by pleural effusion) and jugular venous distention or pulsation are common. Radiographic and ECG findings usually suggest RV enlargement. Therapy is directed at controlling the signs of heart failure. This includes thoracocentesis as needed, cage rest, and cautious furosemide therapy (e.g., 1 mg/kg q12-24h). An ACEI may be helpful. Digoxin is not usually recommended. Pimobendan might be considered, but clinical experience is lacking. The cat's clinical progress and clinicopathologic abnormalities are used to guide supportive therapy.

Caval syndrome occurs rarely in cats. Successful removal of adult worms through a jugular venotomy is possible.

Adulticide therapy may be considered for cats that continue to manifest clinical signs despite prednisone treatment. Potentially fatal thromboembolism can occur, even with only one worm present. About a third of adulticide-treated cats are expected to have thromboembolic complica-

tions. The risk is expected to be higher for heavily infected cats. An adulticide should never be given only on the basis of a positive Ag, Ab, or microfilaria test result. There is little clinical experience with melarsomine (Immiticide) in cats. Doses of >3.5 mg/kg appear to be toxic in this species. IV thiacetarsamide (Caparsolate) has been used successfully at the same doses used in dogs (2.2 mg/kg q12h for 2 days) in combination with prednisone and extremely close monitoring for 2 weeks. Acute respiratory failure and death may occur as a result of dying worms or toxic effects of the arsenical drug. Profound depression and GI side effects also are common after each dose. Pretreatment with an antihistamine and soluble glucocorticoid before thiacetarsamide administration is of unknown efficacy. The effectiveness of chronic ivermectin at the recommended prophylactic dose against juvenile worms in cats is not known. Results of adult worm Ag tests should be negative within 3 to 4 months of successful adulticide therapy; the time required for Ab titers to become negative is likely much longer.

#### SURGICAL THERAPY

Several approaches are described for removing adult heartworms from cats, although they are technically challenging. A right jugular venotomy may be used to reach worms in the right atrium and vena cava with small alligator forceps, endoscopic grasping or basket retrieval forceps, or another device. Worm removal via thoracotomy and right atriotomy has also been done successfully. A left thoracotomy and pulmonary arteriotomy may permit worm extraction from within the pulmonary artery. A potentially fatal anaphylactic reaction associated with worm breakage could occur during such procedures. Presurgical treatment with a glucocorticoid and antihistamine has been suggested. It is not known whether pretreatment with heparin for several days can reduce thromboembolism associated with surgical worm removal.

#### MICROFILARICIDE THERAPY

Microfilaricide therapy is rarely necessary because microfilaremia is brief. However, ivermectin and milbemycin should be effective in this setting.

#### **Heartworm Prevention in Cats**

Heartworm prophylaxis is recommended for cats in endemic areas. Selamectin (Revolution), ivermectin (Heartgard for cats), and milbemycin oxime (Interceptor Flavor Tabs for Cats) are effective preventive drugs in cats. Selamectin is used at the same dose as for dogs (6-12 mg/kg, topically). Selamectin also is useful for controlling fleas and earmites as well as hookworm and roundworm infections in cats. Ivermectin is administered orally at 24 µg/kg monthly (four times the dose used in dogs). The minimum recommended dose for milbemycin is 2 mg/kg (about twice the dose used in dogs). All these agents are safe in kittens 6 weeks or older. A heartworm Ag test is recommended before beginning prophylaxis if infection could have occurred 8 months or more in the past. These agents may be used in seropositive cats.

The efficacy of moxidectin or DEC for heartworm prevention in cats is not known.

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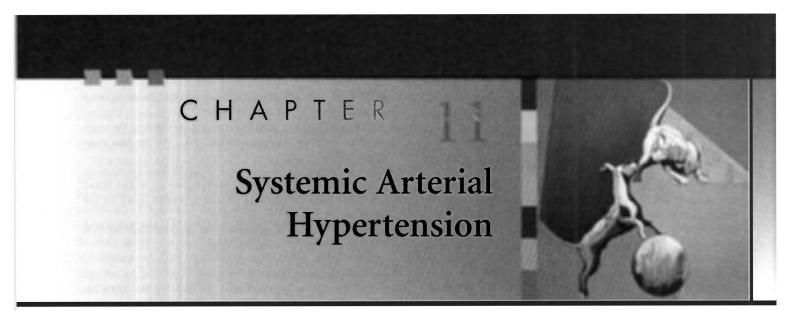
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#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
Blood Pressure Measurement
Antihypertensive Drugs
Hypertensive Emergency

#### **GENERAL CONSIDERATIONS**

Over time, marked elevation of arterial blood pressure (BP) can cause serious clinical consequences. Various factors influence values obtained for systolic, diastolic, and mean arterial BP in healthy animals. Breed-related variation and variations related to age, gender, reproductive status, and other factors can occur. An average normal BP across breeds of dog is about 133/75 mm Hg (systolic/diastolic), and an average normal BP in cats is about 124/84 mm Hg, using oscillometric methods. However, breed-related variations should always be taken into account; for example, because Greyhounds have higher systolic BP and Irish Wolfhounds lower systolic BP than other breeds, the recommendations of the Veterinary Blood Pressure Society should be interpreted with caution. Variation in measured BP may be related to technique (direct and various noninvasive methods) as well as to patient anxiety. Systolic BP can exceed 180 mm Hg in some stressed normal animals. The demarcation between acceptable and "abnormally high" arterial BP is not clear-cut. Furthermore, although some dogs and cats clearly have clinical disease caused by hypertension, many with "abnormally high" BP have no evidence of related pathology, although a predisposing disease condition may exist. Repeated BP measurements over time along with careful clinical evaluation are indicated when considering a diagnosis of hypertension.

Guidelines from the Veterinary Blood Pressure Society suggest that repeatable (on at least three occasions) pressure measurements of 150 to 160 mm Hg systolic and 95 to 100 mm Hg diastolic constitute mild hypertension; an additional 20 mm Hg is allowed for specific breed differences

(e.g., for some sight hounds). Moderate hypertension is associated with BPs between 160 and 180 mm Hg systolic and 100 and 120 mm Hg diastolic (plus ~30 mm Hg for specific breed differences). Arterial pressures >180/120 mm Hg (plus ~50 mm Hg for specific breeds) indicate severe hypertension.

Mild hypertension generally does not require antihypertensive therapy, although any underlying disease should be addressed. Some animals with moderate hypertension also may not need specific antihypertensive therapy. However, severe hypertension should be treated to prevent or reduce end-organ damage. Some animals require urgent antihypertensive therapy (see p. 190). If antihypertensive therapy is used, close monitoring for efficacy, adverse effects, and deterioration of underlying conditions is warranted.

#### Etiology

Hypertension is usually associated with other diseases (Box 11-1) rather than being a primary condition (idiopathic or essential hypertension) in dogs and cats. There is a high prevalence of at least mild hypertension in cats with renal disease or hyperthyroidism. Renal disease, especially involving glomerular function, and hyperadrenocorticism are commonly associated with hypertension in dogs; diabetes mellitus, hypothyroidism, and liver disease may also be associated with higher BP. Because of the increased risk for hypertension in patients with such conditions, BP should be measured when diagnosing the disease as well as periodically thereafter. Similarly, hypertension discovered during a routine exam may be an early marker of such underlying disease. Certain drugs, such as glucocorticoids, mineralocorticoids, nonsteroidal antiinflammatory agents, phenylpropanolamine, sodium chloride, and even topical ocular phenylephrine, can increase BP. Obesity is known to increase BP mildly in dogs. Inherited idiopathic (essential) hypertension has been documented in dogs and cats, but it is uncommon. Idiopathic hypertension is considered a diagnosis of exclusion.

#### **Pathophysiology**

BP depends on the relationship between cardiac output and peripheral vascular resistance. BP is increased by conditions



BOX 11-1

#### Diseases Associated with Hypertension

#### Documented or Suspected Causes in Dogs and Cats

Renal disease (tubular, glomerular, vascular)

Hyperadrenocorticism

Hyperthyroidism

Pheochromocytoma

Diabetes mellitus

Liver disease

Hyperaldosteronism

Intracranial lesions (1 intracranial pressure)

High-salt diet (?)

Obesity

Chronic anemia (cats)

#### Other Diseases Associated with Hypertension in People\*

Acromegaly

Inappropriate antidiuretic hormone secretion

Hyperviscosity/erythrocytosis

Renin-secreting tumors

Hypercalcemia

Hypothyroidism with atherosclerosis

Hyperestrogenism

Coarctation of the aorta

Pregnancy

Central nervous system disease

that raise cardiac output (by increasing heart rate, stroke volume, and/or blood volume) or by those that increase vascular resistance. Arterial BP normally is maintained within narrow bounds by the actions of the autonomic nervous system (e.g., via arterial baroreceptors), various hormonal systems (e.g., the renin-angiotensin system [RAAS], aldosterone, vasopressin/antidiuretic hormone, and natriuretic peptides), blood volume regulation by the kidney, and other factors.

Modulation of these systems by various disease conditions can lead to chronic elevation of arterial BP. For example, hypertension can result from increased sympathetic nervous activity or responsiveness (e.g., hyperthyroidism, hyperadrenocorticism), increased catecholamine production (e.g., pheochromocytoma), or volume expansion caused by increased sodium retention (e.g., decreased glomerular filtration and reduced sodium excretion in renal failure, hyperaldosteronism, hyperadrenocorticism, acromegaly). RAAS activation, with subsequent salt and water retention and vasoconstriction, may result from intrarenal diseases (e.g., glomerulonephritis, chronic interstitial nephritis), enhanced production of angiotensinogen (e.g., hyperadrenocorticism), and extrarenal diseases that increase sympathetic nervous activity or interfere with renal perfusion (e.g., hyperthyroidism, renal artery obstruction). Impaired production of vasodilator substances (e.g., prostaglandins, kallikreins) and



BOX 11-2

#### Complications of Hypertension

#### Ocular

Retinopathy (edema, vascular tortuosity, hemorrhage, focal ischemia, atrophy)

Choroidopathy (edema, vascular tortuosity, hemorrhage, focal ischemia)

Retinal detachment (bullous or total)

Hemorrhage (retinal, vitreal, hyphema)

Papilledema

Blindness

Glaucoma

Secondary corneal ulcers

#### Neurologic

Edema, 1 intracranial pressure

Hypertensive encephalopathy (lethargy, behavioral changes) Cerebrovascular accident (focal ischemia, hemorrhage) Seizures or collapse episodes

#### Renai

Polyuria/polydipsia Glomerulosclerosis/proliferative glomerulitis Renal tubular degenerative and fibrosis Further deterioration in renal function

#### Cardiac

Left ventricular hypertrophy (overt heart failure rare) Murmur or gallop sound Aortic dilation

Aortic dilation

Aneurysm or dissection rare

#### Other

**Epistaxis** 

effects related to secondary hyperparathyroidism may be involved in chronic renal failure.

High perfusion pressure can damage capillary beds. In most tissues capillary pressure is regulated by vasoconstriction of arterioles that feed the capillaries, although this control may be inadequate because of underlying organ disease. The continued arteriolar constriction secondary to chronic hypertension leads to hypertrophy and other vascular remodeling changes that can further increase vascular resistance. These structural changes and vascular spasm can cause capillary hypoxia, tissue damage, hemorrhage, and infarction, which can lead to organ dysfunction (Box 11-2).

Organs that are particularly vulnerable to damage resulting from chronic hypertension are the eye, kidney, heart, and brain. These structures are often referred to as *target-organs* or *end-organs*. In the eye hypertension often causes focal perivascular edema, hemorrhage, and ischemia, especially in the retina and choroid layers. Bullous or total retinal detachment is common. Hyphema, vitreal hemorrhage, and optic neuropathy can also occur. Renal glomerular hypertension

<sup>\*</sup>Essential hypertension is often associated with family history, high salt intake, smoking, or obesity.

occurs when afferent arteriolar autoregulation is disrupted. The resulting glomerular hyperfiltration can lead to glomerulosclerosis, renal tubular degeneration, and fibrosis. These changes contribute to renal function deterioration and increasing vascular resistance; thus chronic hypertension tends to perpetuate itself. Proteinuria is an important manifestation of renal damage and has been associated experimentally with severity of hypertension in cats and dogs. Blood pressure is not directly correlated with serum creatinine concentrations, and hypertension can develop prior to azotemia. Increased systemic arterial pressure and vascular resistance increase the afterload stress on the heart and stimulate left ventricular hypertrophy. Increased cerebral vascular pressure can promote edema formation, raise intracranial pressure, and cause hemorrhage.

#### **Clinical Features**

Clinically recognized arterial hypertension usually occurs in middle-aged to older dogs and cats, presumably because of the associated disease conditions. Cats with severe end-organ disease secondary to hypertension tend to be geriatric. Signs of hypertension relate either to underlying disease or to endorgan damage caused by the hypertension itself.

Ocular signs are the most common presenting issue, especially sudden blindness, which usually results from acute retinal hemorrhage or detachment. Although the retina may reattach, sight often does not return. Ocular fundic changes associated with hypertension include bullous to complete effusive retinal detachment, intraretinal edema, and hemorrhage. Vascular tortuosity, hyperreflective scars, retinal atrophy, papilledema, and perivasculitis are other signs. Hemorrhage in the anterior or posterior chamber, closed-angle glaucoma, and cornal ulceration may also occur.

Another common complaint is polyuria and polydipsia, which can be associated with renal disease, hyperadrenocorticism (in dogs), or hyperthyroidism (in cats). Furthermore, hypertension itself causes a so-called pressure diuresis. Epistaxis can result from vascular rupture in the nasal mucosa. Hypertensive encephalopathy resulting from edema and vascular lesions can cause lethargy, seizures, abnormal mentation, collapse, or other neurologic or nonspecific signs. Paresis and other focal defects can occur as a result of cerebrovascular accident (stroke) caused by hypertensive arteriolar spasm or hemorrhage.

A soft, systolic cardiac murmur is commonly heard on auscultation in animals with hypertension. A gallop sound may also be present, especially in cats. Clinical heart failure is uncommon.

#### Diagnosis

Blood pressure measurements are indicated not only when signs compatible with hypertension are found but also when a disease associated with hypertension is diagnosed. A diagnosis of arterial hypertension should be confirmed by measuring BP multiple times and on different days. A routine laboratory database (complete blood count [CBC]; serum biochemical profile; and urinalysis, with or without a urine

protein: creatinine ratio [UPC]) is indicated in all hypertensive patients. However, not all hypertensive patients with underlying chronic renal disease are azotemic. Other tests are done as needed to rule out possible underlying diseases or complications. These might include various endocrine tests, thoracic and abdominal radiographs, ultrasonography (including echocardiography), electrocardiography, ocular examination, and serologic tests.

Thoracic radiographs often reveal some degree of cardiomegaly in patients with chronic hypertension. Cats especially may have a prominent aortic arch and an undulating (wavy) appearance to the thoracic aorta, although these findings may not be exclusive to hypertension. Electrocardiographic (ECG) findings may suggest left atrial (LA) or left ventricular (LV) enlargement. Arrhythmias do not appear to be common.

Mild to moderate LV hypertrophy is seen on echocardiography in some cases, although often measurements are within normal reference range. LV wall and septal hypertrophy may be symmetric or asymmetric. Other echocardiographic findings may include mild LA enlargement and sometimes mitral or mild aortic regurgitation. Proximal aortic dilation is another echocardiographic finding in some animals with systemic hypertension. Nelson et al. (2002) found that almost all hypertensive cats, but not healthy older cats, had a ratio of proximal ascending aortic diameter: aortic valve annulus diameter of ≥1.25.

#### **BLOOD PRESSURE MEASUREMENT**

Several methods can be used to measure systemic arterial BP in the clinic. Calculating the average of several measurements (generally between three and five) in succession is recommended to increase accuracy. When readings differ widely, the highest and lowest are discarded and an average value from at least three readings is used. High pressures should be confirmed by repeated measurement sessions before a diagnosis of hypertension is made. Anxiety related to the clinical setting may falsely increase blood pressure in some animals (i.e., the "white-coat effect"). Using the least restraint possible in a quiet environment and allowing time (e.g., 5 to 15 minutes) for acclimatization is best for awake animals. Use of a consistent technique and cuff size is important.

#### **Direct Blood Pressure Measurement**

Arterial pressure is measured directly by a needle or catheter placed into an artery and connected to a pressure transducer. Direct arterial pressure measurement is considered the gold standard, but it requires greater technical skill; moreover, in awake animals the physical restraint and discomfort associated with arterial puncture may falsely increase BP. Direct arterial pressure measurement is more accurate than indirect methods in hypotensive animals.

For arterial pressure monitoring over a period of time, an indwelling arterial line is often the best approach. The dorsal metatarsal artery is commonly used for this technique. An electronic pressure monitor provides continuous measure-

ment of systolic and diastolic pressures and calculated mean pressure. With fluid-filled systems, the pressure transducer must be placed at the level of the patient's right atrium to prevent a false increase or decrease of the measured pressure related to the effects of gravity on the fluid within the connecting tubing. The use of wireless, telemetric blood pressure monitors for dogs is currently under investigation.

When occasional BP measurement is needed, a small-gauge needle attached directly to a pressure transducer may be used to puncture the dorsal metatarsal or femoral artery. To prevent hematoma formation, direct pressure should be applied to the arterial puncture site for several minutes after removing the catheter or needle used for BP measurement.

#### **Indirect Blood Pressure Measurement**

Several noninvasive methods are available to indirectly measure BP. These techniques involve the use of an inflatable cuff that is placed around a limb, usually the radial artery (most dogs) or brachial artery (small dogs and cats) or the median caudal artery of the tail to occlude blood flow. Controlled release of cuff pressure is monitored to detect the return of flow. Doppler ultrasonic flow detection and oscillometric methods are used most often. Both techniques produce measurements that correlate fairly well with direct BP measurement but are not exactly predictive of it. Indirect methods are most reliable in normotensive and hypertensive animals. The Doppler method has shown greater correlation with direct BP measurement in conscious cats compared with the oscillometric method. Other methods, such as auscultation and arterial palpation, are not recommended for estimating BP. The auscultatory method (used to detect Korotkoff sounds in people) is technically impractical because of the limb conformation of dogs and cats. Direct arterial palpation is not reliable for estimating BP because pulse strength depends on the pulse pressure (systolic minus diastolic arterial pressure), not the absolute level of systolic or mean pressure. Pulse strength is also influenced by body conformation and other factors.

Cuff size and placement. Human pediatric- and infant-size cuffs can be used for indirect BP measurement in dogs and cats. The cuff must be the correct size for the patient. The width of the inflatable balloon (bladder) within the cuff should be about 30% (especially for cats) to 40% (especially for dogs) of the circumference of the extremity it surrounds. The length of the balloon should cover at least 60% of this circumference. Some of the cuff inflation pressure goes toward tissue compression. Cuffs that are too narrow are more affected by this phenomenon and produce falsely increased pressure readings; cuffs that are too wide may underestimate BP. The cuff bladder should be centered over the target artery. Common cuff locations are midway between the elbow and carpus or in the tibial region; skeletal prominences are avoided. The cuff should encircle the limb snugly without being excessively tight. Tape (not just Velcro on the cuff) is used to secure the cuff in position.

**Oscillometric method.** The indirect oscillometric method uses an automated system for detecting and process-

ing cuff pressure oscillation signals. Veterinary models are available (e.g., Cardell Veterinary Blood Pressure Monitor, Sharn, Inc; Memoprint, S&B medVET). With these systems the flow occlusion cuff is inflated to a pressure above the systolic pressure and then slowly deflated in small pressure decrements. The microprocessor measures and averages the resulting pressure oscillations that are characteristic of systolic, diastolic, and/or mean pressures (depending on the system). Accurate results with oscillometric methods depend on careful adherence to the directions for use and an immobile subject. Because muscle contraction can produce oscillations, the limb used should not be bearing weight. At least five readings should be obtained; the lowest and highest are discarded, and the remaining measurements are averaged. The oscillometric method may be difficult to use effectively in small dogs and cats; underestimation of systolic BP is

**Doppler ultrasonic method.** This method employs the frequency change between emitted ultrasound and returning echoes (from moving blood cells or vessel wall) to detect blood flow in a superficial artery. This frequency change, the so-called Doppler shift, is converted to an audible signal. One system commonly used in animals is designed to determine systolic pressure by detecting blood cell flow (Ultrasonic Doppler Flow Detector, Model 811, Parks Medical Electronics, Inc).

Effective locations for pressure measurement include the dorsal metatarsal, palmar common digital (forelimb), and median caudal (tail) arteries. The probe is placed distal to the occluding cuff. A small area of hair is clipped over the artery for probe placement. Ultrasonic coupling gel is applied to the flat Doppler flow probe to obtain air-free contact with the skin. The probe is positioned so that a clear flow signal is heard; it must not be held so tightly that it occludes flow. The probe must remain still to minimize noise; it can be taped in place. A low volume setting on the Doppler unit or a headset is used to minimize patient anxiety caused by the loud audio signals.

The flow-occluding cuff is attached to a sphygmomanometer and inflated to about 20 to 30 mm Hg above the point at which arterial flow ceases and no audible signals are heard. The cuff is slowly deflated (by a few mm Hg per second). During deflation, characteristic pulsatile flow signals from blood cell (or arterial wall) motion return during systole. The systolic pressure is the pressure at which blood flow first recurs (indicated by brief swishing sounds). Sometimes a change in the flow sound from short and pulsatile to a longer, more continuous swishing can be detected as cuff pressure diminishes; the pressure at which this change occurs is an approximation of diastolic pressure. Doppler estimation of diastolic BP is less accurate because of its subjective nature. The change in flow sound is not always detectable, especially with small or stiff vessels. As with the oscillometric method, it may be difficult to obtain measurements in small or hypotensive animals with the Doppler method. Patient movement also interferes with measurement.

#### Treatment and Prognosis

Antihypertensive therapy is indicated for animals with severe hypertension and those with clinical signs presumed to be caused by hypertension. Measured BP in such animals is generally over 180/120 mm Hg. Although some cases constitute hypertensive emergencies that require immediate therapy and intensive monitoring (discussed in more detail later), most hypertensive animals can be managed more conservatively (Box 11-3). Gradual reduction in BP may be safer in patients with long-standing hypertension. Chronically high BP leads to vascular adaptations in the cerebral autoregulatory process; if BP is suddenly reduced, cerebral perfusion may be adversely affected. It is unclear whether all dogs and cats with moderate hypertension (e.g., repeatable systolic pressures of 160 to 180 mm Hg) benefit from specific antihypertensive treatment. Nevertheless, patients with high BP that persists after treatment for the primary disease, as well as those with evidence of end-organ damage, should be treated. The goal of therapy is to reduce the BP to below 150/95 mm Hg. The expense and time commitment required for long-term antihypertensive therapy and monitoring as well as the potential for adverse medication effects are considerations.

Several drugs are used as antihypertensive agents in dogs and cats (Table 11-1). Usually one drug is administered at a time, with initially low doses, and the animal is monitored to assess efficacy. It may take 2 or more weeks for a significant decrease in BP to be observed. The drugs used most often are angiotensin-converting enzyme inhibitors (ACEIs), the Ca<sup>++</sup>-blocker amlodipine, and β-adrenergic blockers. Therapy with a single agent is effective in some cases, whereas combination therapy may be needed for adequate BP control in others. An ACEI is recommended as the initial antihypertensive drug in dogs, and amlodipine in cats, unless hyperthyroidism is the underlying cause. For hyperthyroid-induced hypertension, atenolol or another β-blocker is used first.

Ancillary strategies may be helpful in patients with hypertension, although alone they are unlikely to markedly reduce BP. Moderate dietary salt reduction (e.g., ≤0.22% to 0.25%



BOX 11-3

Approach to the Patient with Hypertension

#### Suspect Hypertension or Disease Associated with Hypertension (see Box 11-2, text)

Measure BP (see text)

- Use quiet environment.
- Allow at least 5 to 10 minutes for patient to acclimate to environment (if animal is easily stressed, have owner present when possible).
- Measure limb circumference, and use appropriate-size cuff (use same cuff size for subsequent measurements as well).
- Use consistent measurement technique.
- Take at least five BP readings; discard highest and lowest, average the remaining readings.

Repeat BP measurements at other (one to three) times, preferably on different days, to confirm diagnosis of hypertension, except:

 If acute, hypertension-induced clinical signs (e.g., ocular hemorrhage, retinal detachment, neurologic signs) are present, begin therapy immediately (see p. 190; Table 11-1).

Screen for underlying disease(s) (see Box 11-1)

- Obtain CBC, serum biochemistry tests, urinalysis.
- Obtain other data depending on individual presentation: endocrine testing, thoracic and abdominal radiographs, ocular examination, ECG, echocardiography, other tests as indicated.

#### **If Hypertension Confirmed:**

Manage underlying disease(s).

Avoid drugs that can increase BP, if possible.

Use reduced-sodium or weight reduction diet if patient is

Begin initial antihypertensive drug therapy (see Table 11-1).

- Dogs: enalapril or other ACEL
- If pheochromocytoma suspected, see p. 190
- Nonhyperthyroid cats: amlodipine
- Hyperthyroid cats: atenolol or other β-blocker
- If emergent therapy needed, see p. 190

Provide client education about the patient's disease(s) and potential complications, medication and reevaluation schedules, potential adverse effects of medication(s), and dietary concerns.

#### Patient Reevaluation

Recheck BP in 1 to 2 weeks for clinically stable patients.

 Earlier reevaluation is advised for unstable patients, but full effects of antihypertensive drugs may not yet be realized.

Obtain other tests as individually indicated.

Decide whether to continue therapy as is or adjust dose (up or down).

Continue weekly to biweekly BP monitoring and underlying disease management.

 If BP control is not achieved after maximum dosage of initial agent, try alternative drug or combination therapy.

When BP (and underlying disease) is controlled, gradually increase time between recheck examinations.

- Recheck no less frequently than every 2 to 3 months because medication requirements may change.
- Recheck baseline lab data every 6 months or as individually indicated.



#### Drugs Used to Treat Hypertension

DRUG	DOG	CAT
ACEIs (see Chapter 3)		
Enalapril Benazepril Ramipril Captopril	0.5 mg/kg PO q24(-12)hr 0.25-0.5 mg/kg PO q24(-12)hr 0.125-0.25 mg/kg PO q24hr 0.5-2.0 mg/kg PO q8-12hr	0.25-0.5 mg/kg PO q24hr same — 0.5-1.25 mg/kg PO q12-24hr
Calcium Channel Blocker		
Amlodipine	0.1-0.3 (-0.5) mg/kg PO q24(-12)hr	0.625 mg/cat (or 0.1-0.2 mg/kg) PO q24(-12)hr
β-Adrenergic Blockers (see Chap	oter 4)	
Atenolol Propranolol	0.2-1.0 mg/kg PO q12-24hr (start low) 0.1-1.0 mg/kg PO q8hr (start low)	6.25-12.5 mg/cat PO q(12-)24hr 2.5-10 mg/cat PO q8-12hr
α <sub>1</sub> -Adrenergic Blockers		
Phenoxybenzamine Prazosin	0.2-1.5 mg/kg PO q(8-)12hr 0.05-0.2 mg/kg PO q8-12hr	0.2-0.5 mg/kg PO q12hr —
Diuretics (see Chapter 3)		
Furosemide Hydrochlorothiazide	0.5-3 mg/kg PO q8-24hr 1-4 mg/kg PO q12-24hr	0.5-2 mg/kg PO q12-24hr 1-2 mg/kg PO q12-24hr
Drugs for Hypertensive Crisis		
Hydralazine (see Chapter 3)	0.5-2.0 mg/kg PO q12h (titrate up to effect); or 0.2 mg/kg IV or IM, repeat q2h as needed	same
Nitroprusside (see Chapter 3)	0.5-1 μg/kg/min CRI (initial) to 5-15 μg/kg/min CRI	same
Enalaprilat Esmolol Propranolol Labetolol	0.2 mg/kg IV, repeat q1-2h as needed 50-75 μg/kg/min CRI 0.02 mg/kg (initial) to 0.1 mg/kg slow IV 0.25 mg/kg IV over 2 min, repeat up to total dose of 3.75 mg/kg, followed by CRI of 25 μg/kg/min	same same same
Acepromazine Phentolamine	0.05-0.1 mg/kg (up to 3 mg total) IV 0.02-0.1 mg/kg IV bolus, followed by CRI to effect	same same

ACEI, Angiotensin-converting enzyme inhibitor; PO, by mouth; IV. intravenous; CRI, constant rate infusion.

sodium on a dry matter basis) is advised for all cases. Although not expected to normalize BP by itself, it may enhance antihypertensive drug effectiveness. A high-salt diet may contribute to development of hypertension in some cats, although salt intake does not generally affect BP in normal cats. Conversely, neurohormonal activation and potassium excretion may be increased in cats with renal dysfunction that are fed a low-sodium diet. Weight reduction is usually advised for obese animals. It is prudent to avoid prescribing drugs that can potentiate vasoconstriction (e.g., phenylpropanolamine and other  $\alpha_1$ -adrenergic agonists). Glucocorticoids and progesterone derivatives should also be avoided when possible because steroid hormones can increase BP. A diuretic (thiazide or furosemide; see Chapter 3) may help by reducing blood volume in patients with volume expansion, but a diuretic alone is rarely effective. Diuretics are avoided or used only with caution in animals with renal disease because they can lead to dehydration and exacerbate azotemia. Serum potassium concentration should be monitored, especially in cats with chronic renal disease.

The ability to monitor BP is important when antihypertensive drugs are prescribed. Serial measurements are needed to assess treatment efficacy and prevent hypotension. Adverse effects of antihypertensive therapy usually relate to hypotension, manifested by lethargy or ataxia, and reduced appetite. Attaining initial BP control may take several weeks. Monitoring may be done every 1 to 2 weeks to assess the efficacy of antihypertensive treatment in non-urgent cases. Once satisfactory regulation is achieved, BP should be measured at least every 2 or 3 months. Some animals become refractory to therapy that was initially effective. Increased antihyper-

tensive dosage, adjunctive therapy, or a change of antihypertensive drug can be tried. Continued attention to the underlying disease process is important. Routine CBC, serum biochemistry profile, and urinalysis (with or without a UPC) are also recommended every 6 months. Decreasing the magnitude of proteinuria associated with hypertension is a desired treatment outcome.

The long-term prognosis for animals with hypertension is usually guarded because underlying disease processes tend to be severe and progressive. Therapy for some primary diseases can exacerbate hypertension or complicate its control. Fluid therapy, corticosteroids, and erythropoietin are examples. The degree of proteinuria appears to be a negative prognostic factor in cats with chronic renal disease.

#### ANTIHYPERTENSIVE DRUGS

The ACEIs (e.g., enalapril, benazepril) reduce angiotensin II production, thereby reducing vascular resistance and volume retention (see p. 63). These agents have been more effective in dogs, although their efficacy depends on the degree of RAAS activation underlying the hypertension. Cats with chronic kidney disease and hypertension often are not responsive to ACEIs. However, an ACEI may help protect against hypertensive renal damage by preferentially reducing efferent arteriolar constriction and reducing glomerular hypertension.

Amlodipine besylate is a long-acting dihydropyridine  $Ca^{++}$ -blocker that causes vasodilation without appreciable cardiac effects. It can be effective as a primary antihypertensive agent in cats and has a duration of effect of at least 24 hours. Amlodipine generally does not alter serum creatinine concentration or body weight in cats with chronic kidney disease. Mild hypokalemia should respond to oral potassium supplementation. The drug is usually dosed once daily and may be given with or without food. Administration q12h may be used in large cats or in those that do not respond sufficiently to the lower dose. Alternatively, a  $\beta$ -blocker or ACEI may be added for cats that do not respond adequately to amlodipine alone. Amlodipine tablets are difficult to split evenly but they can be compounded using lactose as a diluent.

Amlodipine also is effective in some dogs. A lower dose is tried initially and titrated upward as necessary over a period of days. Amlodipine's half-life is about 30 hours in dogs; maximal effects occur 4 to 7 days after initiating therapy. Oral bioavailability is high, and peak plasma concentrations are reached 3 to 8 hours after administration; plasma concentrations increase with chronic therapy. The drug undergoes hepatic metabolism, but there is not extensive first-pass elimination; caution is warranted when liver function is poor. The drug is excreted through the urine and feces. A Ca'-channel blocker used as adjunctive therapy with an ACEI in dogs may control BP while yielding a balanced effect on glomerular pressure and glomerular filtration rate (GFR) through equal dilation of afferent and efferent arterioles.

 $\beta$ -adrenergic blockers may reduce BP by decreasing heart rate, cardiac output, and renal renin release. Atenolol and propranolol have been used most often (see p. 89). A  $\beta$ -blocker is recommended for cats with hyperthyroid-induced hypertension. However,  $\beta$ -blockers are often ineffective when used as the sole antihypertensive agent in cats with renal disease.

 $\alpha_1$ -adrenergic antagonists oppose the vasoconstrictive effects of these  $\alpha$ -receptors. Their main use is for hypertension caused by pheochromocytoma. Phenoxybenzamine is a noncompetitive  $\alpha_1$ - and  $\alpha_2$ -blocker used most often for pheochromocytoma-induced hypertension. Treatment is initiated with a low dose that is titrated upward as necessary. The  $\alpha_1$ -blocker prazosin is another option for large dogs. After  $\alpha$ -blocker dosing is begun, adjunctive therapy with a  $\beta$ -blocker can help control reflex tachycardia or arrhythmias.

Hypotension is a potential adverse effect of antihypertensive drugs and is usually manifested as periods of lethargy or ataxia. Reduced appetite may be another adverse effect. Rebound hypertension can occur if antihypertensive therapy is suddenly discontinued. This is especially of concern when using  $\beta$ - or  $\alpha_2$ -blockers. If therapy with such agents is to be terminated, the dosage should be gradually tapered down.

#### HYPERTENSIVE EMERGENCY

Urgent antihypertensive therapy is indicated when new or progressive signs of severe hypertension are identified. Examples include acute retinal detachment and hemorrhage, encephalopathy, or other evidence of intracranial hemorrhage, acute renal failure, aortic ancurysm, and acute heart failure.

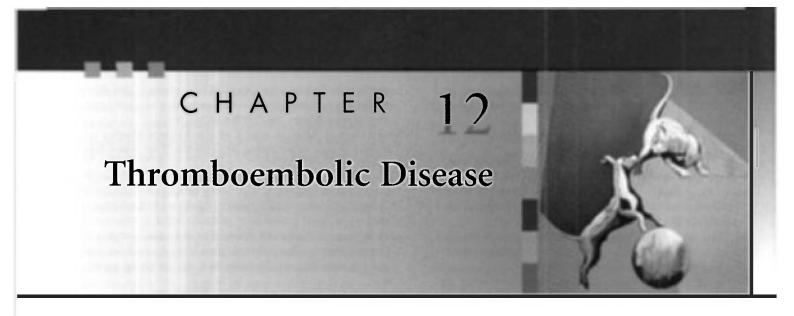
Direct-acting vasodilator agents generally produce faster reduction in BP (e.g., nitroprusside, hydralazine). Nitroprusside can be dosed to effect by constant intravenous (IV) infusion, but arterial pressure should be closely monitored to prevent hypotension (see Table 11-1). Hydralazine given intravenously or orally is an alternative, especially for dogs. Oral amlodipine can be effective in quickly reducing blood pressure in cats and has less risk of inducing hypotension. An IV  $\beta$ -blocker (propranolol, esmolol, or labetolol), ACEI (enalaprilat), or acepromazine (see Table 11-1) also can be used. One of these agents can be added to oral hydralazine therapy if that has not adequately reduced BP within 12 hours.

When hypertensive crisis is related to pheochromocytoma or other cause of catecholamine excess, the  $\alpha$ -blocker phentolamine is used IV (see Table 11-1) and titrated to effect. Addition of a  $\beta$ -blocker can help mitigate pheochromocytoma-induced tachyarrhythmias, but it should not be administered alone or before an  $\alpha$ -blocker is given. Use of a  $\beta$ -blocker as the sole agent in this setting leaves  $\alpha_1$ -receptors unopposed and is likely to exacerbate hypertension. Antihypertensive treatment is recommended for 2 to 3 weeks before surgery for pheochromocytoma excision, if possible. For inoperable pheochromocytoma, therapy is continued orally to prevent hypertensive emergencies.

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# CHAPTER OUTLINE

GENERAL CONSIDERATIONS
PULMONARY THROMBOEMBOLISM
SYSTEMIC ARTERIAL THROMBOEMBOLISM IN CATS
Prophylaxis Against Arterial Thromboembolism
SYSTEMIC ARTERIAL THROMBOEMBOLISM IN DOGS
Prophylaxis against Arterial Thromboembolism
VENOUS THROMBOSIS

#### GENERAL CONSIDERATIONS

Thromboembolic (TE) disease involves either a locally formed (*in situ*) clot, an aggregation of platelets and other blood elements (thrombus), or a clot or other aggregate that breaks away from its origination site (embolus) and is carried downstream by blood flow. Both thrombi and emboli can partially or completely obstruct blood flow, either in a vessel or in the heart. TE disease can occur whenever normal hemostatic mechanisms are disturbed. Most clinically recognized TE events involve the distal aorta, pulmonary arteries, heart, or cranial vena cava. (For additional information on the pathogenesis of TE, see Chapter 87.)

The clinical sequelae of TE disease depend mainly on the size and location of the clot(s). These factors determine how much functional compromise occurs and in which organs and tissues. Acute, profound clinical signs result from some thrombolemboli. Others cause subclinical tissue damage and varying degrees of pathology. TE disease is sometimes suspected antemortem; in other cases it is discovered at necropsy (or not at all).

There is normally an interplay among the different factors that promote coagulation, inhibit coagulation, and promote fibrinolysis. A proper balance of these factors maintains blood fluidity and minimizes loss when vessels are damaged. Platelets, the vascular endothelium, proteins of the coagulation cascade, and the fibrinolytic system are all involved in normal hemostasis. Injury to the vascular endothelium

quickly induces several reactions that cause vasoconstriction, hemostatic plug formation, and attempts at vascular repair in order to prevent blood loss.

Intact endothelium normally produces factors with antiplatelet, anticoagulant, and also fibrinolytic effects. Antiplatelet substances include nitric oxide and prostacyclin. Nitric oxide inhibits platelet activation and promotes local vasodilation. Prostacyclin also inhibits platelet activation and aggregation, while mediating vascular smooth muscle relaxation. Anticoagulant substances synthesized by intact endothelium include thrombomodulin, protein S, and heparan sulfate. These substances inhibit the coagulation process in a number of ways.

Damaged endothelial cells promote thrombus formation. Although this reduces blood loss in the event of vascular laceration, in other settings TE disease results. Endothelial damage contributes to thrombus formation in several ways. For example, injured endothelial cells release endothelin, which promotes vasoconstriction and decreases local blood flow as well as tissue factor (thromboplastin), which activates the extrinsic pathway of the coagulation cascade.

Exposed subendothelial collagen and other substances stimulate platelet adherence and aggregation. This is followed by platelet activation. Activated platelets release a number of substances that further stimulate the process of platelet aggregation. Fibrinogen binds to surface glycoprotein (gp) IIb/IIIa receptors, which are expressed on activated platelets. Fibrinogen linkage forms a primary platelet plug, which then stabilizes as platelets contract and fibrinogen is converted to fibrin via the action of thrombin (factor IIa) produced by the coagulation cascade.

Both the intrinsic and extrinsic pathways of the coagulation cascade feed into the common pathway to produce thrombin (see Chapter 87). Tissue factor (released from monocytes and damaged cells) stimulates the extrinsic pathway by activating factor VII. The intrinsic pathway amplifies the process; it also modulates fibrinolysis. Thrombin converts fibrinogen into fibrin monomers. These polymerize to soluble fibrin, which then is cross-linked by the action of thrombin-activated factor XIII. This insoluble fibrin stabilizes the clot. Thrombin also stimulates further

platelet aggregation as well as contributes to negative feedback inhibition of clotting by interacting with thrombomodulin, proteins C and S, and antithrombin (AT).

After a thrombus forms, several mechanisms limit its extent and promote its breakdown. Thrombolysis requires plasmin. Its inactive precursor, plasminogen, is converted to plasmin by tissue plasminogen activator (t-PA) when fibrin is present. During activation of the coagulation cascade, t-PA is simultaneously released by endothelial cells. Several other substances also can act as plasminogen activators. Plasmin degrades fibrinogen and soluble (noncrosslinked) fibrin to yield fibrinogen/fibrin degradation products (FDPs). Plasmin also cleaves cross-linked fibrin in stabilized clots into large fragments (x-oligomers) that are further broken down into p-dimers and other fragments. p-dimers are produced only with active coagulation and subsequent fibrinolysis. There are also negative feedback constraints on fibrinolysis (e.g., plasminogen activator inhibitors, α2antiplasmin, thrombin-activated fibrinolytic factor). Defective fibrinolysis is thought to play a role in pathologic thrombosis.

Inhibition of platelet adherence and activation is important in preventing primary platelet plug formation. In addition, there are three main mechanisms that limit thrombus formation: AT, protein C, and the fibrinolytic system. AT is a small protein produced by the liver, which is responsible for most of the anticoagulant effect of plasma. AT, with its co-factor heparan sulfate, binds and inactivates thrombin; factors IXa, Xa, Xia, and XIIa; and kallikrein. Protein C, a vitamin K—dependent glycoprotein, also is involved in countering thrombosis.

Malfunction of one or more of these systems promotes thrombosis.

### **Pathophysiology**

TE disease is more likely when changes in normal hemostatic processes create conditions that favor clot formation or impair thrombolysis. Three general situations (so-called Virchow's triad) promote pathologic thrombosis: abnormal endothelial structure or function, slowed or static blood flow, and a hypercoagulable state (either from increased procoagulant substances or decreased anticoagulant or fibrinolytic substances). A number of common diseases produce such conditions (Box 12-1).

Diseases that induce severe or widespread endothelial injury also cause loss of normal endothelial antiplatelet, anti-coagulant, and fibrinolytic functions. Increased coagulability and platelet activation favor pathologic thrombosis. Injured endothelium also releases tissue factor as well as antifibrinolytic factors. Subendothelial tissue, exposed because of endothelial cell damage, promotes thrombosis by acting as a substrate for clot formation and stimulating platelet adherence and aggregation.

Systemic release of inflammatory cytokines (e.g., tumor necrosis factor [TNF], various interleukins, platelet activating factor, nitric oxide) can cause widespread endothelial injury, induce tissue factor expression, and also inhibit anti-



### BOX 12-1

Diseases Potentially Associated with Thromboembolism

#### **Endothelial Disruption**

Sepsis

Systemic inflammatory disease

Heartworm disease

Neoplasia

Massive trauma

Shock

Intravenous catheterization

Injection of irritating substance

Reperfusion injury

Atherosclerosis

Arteriosclerosis

Hyperhomocysteinemia

#### **Abnormal Blood Flow**

Vascular obstruction (e.g., mass lesion, adult heartworms, catheter or other device)

Heart disease

Cardiomyopathy (especially in cats)

Endocarditis

Congestive heart failure

Shock

Hypovolemia/dehydration

Prolonged recumbency

Hyperviscosity (e.g., polycythemia, leukemia, hyperglobulinemia)

Hypoviscosity (anemia)

Anatomic abnormality (e.g., aneurysm, A-V fistula)

#### Increased Coagulability

Glomerular disease/protein-losing nephropathy

Hyperadrenocorticism

Immune-mediated hemolytic anemia (+/- thrombocytopenia)

**Pancreatitis** 

Protein-losing enteropathy

Sepsis/infection

Neoplasia

Disseminated intravascular coagulation

Heart disease

coagulant mechanisms. This occurs with sepsis and likely other systemic inflammatory conditions as well. Neoplastic invasion, vascular disruption resulting from other disease, and postischemic injury also induce endothelial damage. Mechanical trauma to the vascular endothelium (as with catheterization) can also precipitate TE disease, especially when other predisposing conditions exist. Pulmonary artery endothelial injury resulting from heartworm disease (HWD) is well known (see Chapter 10). The inflammatory reaction to dead or dying worms and worm fragments exacerbates the endothelial damage and prothrombotic conditions.

Stagnant blood flow promotes thrombosis by impeding the dilution and clearance of coagulation factors. Poor flow can promote local tissue hypoxia and endothelial injury as well. Abnormal turbulence has also been associated with thrombus formation. Turbulence can mechanically injure the endothelial surface.

Hypercoagulability may develop secondary to various systemic diseases in dogs and cats; multiple mechanisms are thought to be involved. Nevertheless, thrombus formation in such cases may also depend on altered endothelial integrity or blood flow. AT deficiency is a common cause of hypercoagulability. Excessive loss, increased consumption, or possibly inadequate hepatic synthesis leads to AT deficiency. Decreased protein C activity and other mechanisms may also contribute to hypercoagulability.

Increased platelet aggregability has been associated with neoplasia, some heart diseases, diabetes mellitus, and nephrotic syndrome in some animals. Thrombocytosis alone, without an increase in platelet aggregability, is not thought to increase the risk for thrombosis.

Defective fibrinolysis can promote pathologic thrombosis by preventing efficient breakdown of physiologic clots. This can result from either reduced levels of fibrinolytic substances (e.g., t-PA, plasminogen, urokinase) or increased production of plasminogen activator inhibitors; the latter is a major mechanism of TE disease in humans with hypertension.

Pancreatitis, shock, trauma, sepsis, neoplasia, severe hepatopathy, heatstroke, immune-mediated disease, and other conditions can lead to gross thrombosis as well as disseminated intravascular coagulopathy (DIC). DIC involves massive activation of thrombin and plasmin, with generalized consumption of coagulation factors and platelets. DIC produces extensive thrombosis as well as hemorrhage in the microcirculation, resulting in widespread tissue ischemia and multiorgan failure.

Protein-losing nephropathy (resulting from glomerulo-nephritis, renal amyloid deposition, or hypertensive injury) can lead to marked AT deficiency. Because of its small size, AT is lost through damaged glomeruli more easily than most procoagulant proteins, which predisposes to thrombosis. Protein-losing enteropathies also cause AT deficiency, but concurrent loss of larger proteins tends to maintain a balance between procoagulant and anticoagulant factors. Other factors also may contribute to TE disease in animals with protein-losing nephropathies, such as increased platelet aggregation secondary to hypoalbuminemia.

Thrombosis associated with immune-mediated hemolytic anemia (IMHA) is also thought to be multifactorial, with the systemic inflammatory (immune-mediated) response playing a large role. Thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia have been identified as risk factors for TE disease. The role of high-dose corticosteroid therapy in pathologic thrombosis is unclear. However, TE disease is relatively common in animals receiving exogenous corticosteroids and in those with hyperadrenocorticism (see next paragraph). Other predisposing factors are usually concurrent in these cases as well.

TE disease occurs in some dogs with spontaneous hyperadrenocorticism. This endocrinopathy has been associated

with decreased fibrinolysis (resulting from increased plasminogen activator inhibitor [PAI] activity) and high levels of several coagulation factors. Diabetes mellitus is occasionally associated with TE disease in dogs. Platelet hyperaggregability and possibly hypofibrinolysis are thought to be involved. Occasionally, a patient with clinically relevant TE disease does not have any detectable abnormality that can result in hypercoagulability (e.g., Greyhounds with aortic TE disease not associated with detectable hemostatic or cardiovascular abnormalities). Cats with myocardial disease (see Chapter 8) are at risk for intracardiac thrombus formation and subsequent arterial embolization. The mechanisms involved probably relate to poor intracardiac blood flow (especially within the left atrium), altered blood coagulability, local tissue or blood vessel injury, or a combination of these. Increased platelet reactivity occurs in some of these cats. Abnormal turbulence may be a factor when mitral regurgitation occurs. DIC may accompany thromboembolism. Some cats with TE disease have decreased plasma arginine and vitamin B<sub>6</sub> and B<sub>12</sub> concentrations; hyperhomocysteinemia may be a factor in some cases. Hyperhomocysteinemia and low plasma vitamin B concentrations are risk factors for thromboembolism in people. It is not known if hypercoagulability induced by a genetic abnormality exists in some cats, as it does in people.

#### PULMONARY THROMBOEMBOLISM

Pulmonary thromboemboli in dogs are associated with HWD, other heart diseases, immune-mediated hemolytic anemia (IMHA), neoplasia, DIC, sepsis, hyperadrenocorticism, nephrotic syndrome, pancreatitis, trauma, hypothyroidism, and right atrial thrombus related to infection.

Pulmonary TE disease appears to be rare in cats compared with dogs, except in those with HWD. Nevertheless, pulmonary TE disease has been associated with a variety of systemic and inflammatory disorders in cats, including neoplasia, HWD, anemia (probably immune mediated), pancreatitis, glomerulonephritis, encephalitis, pneumonia, heart disease, sepsis, glucocorticoid administration, protein-losing enteropathy, and hepatic lipidosis.

Pulmonary TE disease that causes pulmonary hypertension variably produces right ventricular enlargement and hypertrophy, interventricular septal flattening, and high tricuspid regurgitation jet velocities. Sometimes a clot is identified within the pulmonary artery or right atrium.

## SYSTEMIC ARTERIAL THROMBOEMBOLISM IN CATS

The most common cause for arterial TE disease in cats is cardiomyopathy (see Chapter 8). Thrombi initially form in the left heart and can become quite large. Although some remain in the heart (usually the left atrial [LA] appendage; see Figure 8-6), others embolize to the distal aorta or, less often, other sites. Marked LA enlargement may magnify the risk for thromboembolus formation, but this is controversial. Neoplastic and systemic inflammatory disease are sometimes associated with systemic thromboemboli in cats. Hyperthyroidism may be a risk factor for TE disease in cats independent of its cardiac effects. In some cases, no predisposing condition is identified.

Systemic arterial emboli usually lodge at the aortic trifurcation (so-called saddle thrombus; Figure 12-1), but iliac, femoral, renal, brachial, and other arteries can be affected depending on embolus size and flow path. Besides obstructing flow in the affected artery, thromboemboli release vasoactive substances that induce vasoconstriction and compromise collateral blood flow development around the obstructed vessel. Tissue ischemia results and causes further damage and inflammation. An ischemic neuromyopathy occurs in the affected limb(s), with peripheral nerve dysfunction and degeneration as well as pathologic changes in associated muscle tissue.

Coronary thromboembolism with myocardial necrosis has occurred in cats with cardiac disease, especially severe hypertrophic cardiomyopathy or infective endocarditis, as well as from carcinoma emboli.

#### **Clinical Features**

Arterial TE disease in cats usually causes acute and dramatic clinical signs secondary to tissue ischemia (Fig. 12-2). Male cats are at higher risk for thromboembolism, but this gender bias appears to be related to the prevalence of hypertrophic cardiomyopathy. Distal aortic embolization occurs in most cases. However, the clinical findings depend on the area embolized as well as the extent and duration of arterial blockage.



FIG 12-1

Postmortem image with opened distal aorta, from a cat with cardiomyopathy. A thromboembolus (just left of the forceps tip) is lodged at the aortic trifurcation. The rear limbs are to the left in the image; cranial is to the right.

Signs of pain and poor systemic perfusion are usually present. Hypothermia and azotemia are common. A cardiac murmur, gallop sound, or arrhythmia is often identified, but these signs are not always evident even with underlying heart disease. Clinical signs of heart disease before the TE event are often absent. Tachypnea and open-mouth breathing are common in cats with acute arterial embolization, despite the absence of overt congestive heart failure (CHF). These signs may represent a pain response, although increased pulmonary venous pressure could be involved. Thoracic radiographs should be obtained as soon as possible because it is important to determine whether pulmonary edema underlies the respiratory signs.

Acute hindlimb paresis without palpable femoral pulses is typical. Common clinical findings are summarized in Box 12-2. Motor function in the rear limbs is minimal to absent in most cases, although the cat is usually able to flex and extend the hips. Sensation to the lower limbs is poor. One side may show greater deficits than the other. Emboli are occasionally small enough to lodge more distally in only one limb, which causes paresis of the lower limb alone. Embolization of a brachial artery produces (usually right) forelimb monoparesis. Intermittent claudication (see p. 201) occurs rarely. Thromboemboli within the renal, mesenteric, or pulmonary arterial circulation may result in failure of these organs and death. Emboli to the brain could induce seizures or various neurological deficits.

#### **Diagnosis**

Thoracic radiography is used to screen for cardiopulmonary abnormalities such as evidence for heart failure or other disease associated with thromboemboli (e.g., glomerulone-phritis, neoplasia, HWD). Most cats with arterial TE disease have some degree of cardiomegaly (especially LA enlargement) when cardiomyopathy is the underlying cause. Signs of heart failure include dilated pulmonary veins, pulmonary edema, or pleural effusion. A few affected cats have no radiographic evidence of cardiomegaly.

Echocardiography delineates the type of myocardial disease and may reveal the presence of an intracardiac thrombus (see Figure 8-6). The most common site for intracardiac thrombi is the left auricular appendage. Most cats with arterial TE disease associated with cardiomyopathy have some degree of LA enlargement. An LA dimension of >20 mm (measured from the two-dimensional long-axis four-chamber view) may increase the risk for TE disease, although more than half of aortic TE disease cases in one study had a smaller left atrium (Smith, 2003). If echocardiography is unavailable, nonselective angiocardiography can help define the nature of underlying cardiac disease and determine the location and extent of the thromboembolism.

Cats with arterial thromboembolism often have azotemia. This can be prerenal, resulting from poor systemic perfusion or dehydration; primary renal, resulting from embolization of the renal arteries or preexisting kidney disease; or a combination of both. Metabolic acidosis, DIC, electrolyte abnormalities (especially low serum sodium, calcium, potassium,





FIG 12-2

**A,** Cat with thromboembolism to the distal aorta. The left rear limb was dragged behind as the cat tried to walk; there was slightly better function in the right rear. **B,** The pads of the left rear paw (right side of image) in this cat were paler as well as cooler compared with the left forepaw (left side of image).



## BOX 12-2

#### Common Clinical Findings in Cats with Systemic Arterial Thromboembolism

Acute limb paresis

Posterior paresis

Monoparesis

±Intermittent claudication

Characteristics of affected limb(s)

Painful

Cool distal limbs

Pale footpads

Cyanotic nailbeds

Absent arterial pulse

Contracture of affected muscles (especially gastrocnemius

and cranial tibial)

Tachypnea/dyspnea

Rule out congestive heart failure versus pain or other

pulmonary disease Vocalization (pain and distress)

Hypothermia

Anorexia

Lethargy/weakness

Signs of heart disease (inconsistent)

Systolic murmur

Gallop sounds

Arrhythmias

Cardiomegaly

Signs of congestive heart failure

Pulmonary edema

Effusions

Hematologic and biochemical abnormalities

Azotemia

Increased alanine aminotransferase activity

Increased aspartate aminotransferase activity

Increased lactate dehydrogenase activity

Increased creatine kinase activity

Hyperglycemia (stress)

Lymphopenia (stress)

Disseminated intravascular coagulation

and elevated phosphorus), and stress hyperglycemia are common. Hyperkalemia may develop secondary to ischemic muscle damage and reperfusion. Skeletal muscle damage and necrosis are accompanied by elevations of alanine aminotransferase and aspartate aminotransferase activities, beginning within 12 hours of the TE event and peaking by 36 hours. Widespread muscle injury causes lactate dehydrogenase and creatine kinase activities to be increased soon after the event; elevations in these enzyme activities may persist for weeks. Metabolic acidosis, DIC, and hyperkalemia may also be present secondary to ischemic muscle damage and reperfusion. Cats with arterial TE disease usually have a normal coagulation profile.

Other causes of acute posterior paresis to be considered include intervertebral disk disease, spinal neoplasia (e.g., lymphoma), trauma, fibrocartilaginous infarction, diabetic neuropathy, and possibly myasthenia gravis.

# **Treatment and Prognosis**

The goals of treatment are to manage concurrent CHF and arrhythmias (if present), prevent extension of the embolus and formation of additional thrombi, promote collateral circulation, and provide supportive care (Box 12-3). The treatment of heart failure is outlined in Chapter 8 and Box 8-1. Propranolol is discouraged in cats with cardiomyopathy and arterial thromboembolism because its nonselective



BOX 12-3

#### Therapy for Thromboembolic Disease

Initial diagnostic tests

Complete physical examination and history
Hemogram, serum biochemical profile, urinalysis
Thoracic radiographs (rule out signs of congestive heart
failure, other infiltrates, pleural effusion)

Coagulation and D-dimer tests, if possible

Analgesia as needed (especially for systemic arterial thromboembolism)

#### Morphine

- Dog: 0.5-2.0 mg/kg administered intramuscularly, subcutaneously q3-5h; 0.05-0.4 mg/kg administered intravenously q3-5h
- Cat: 0.05-0.2 mg/kg administered intramuscularly, subcutaneously q3-4h (dysphoria occurs in some cats)

Oxymorphone or hydromorphone

- Dog: 0.05-0.2 mg/kg administered intramuscularly, intravenously, subcutaneously q2-4h
- Cat: 0.05-0.2 mg/kg administered intramuscularly, intravenously, subcutaneously q2-4h

#### Butorphanol

- Dog: 0.2-2.0 mg/kg administered intramuscularly, intravenously, subcutaneously q1-4h
- Cat: 0.2-1.0 mg/kg administered intramuscularly (cranial lumbar area), intravenously, subcutaneously q1-4h

#### Buprenorphine

- Dog: 0.005-0.02 mg/kg administered intramuscularly, intravenously, subcutaneously q6-8h
- Cat: 0.005-0.02 mg/kg administered intramuscularly, intravenously, subcutaneously q6-8h; can give by mouth for transmucosal absorption

#### Supportive care

Provide supplemental O<sub>2</sub> if respiratory signs exist.

Administer intravenous fluid as indicated (if not in congestive heart failure).

Monitor for and correct azotemia and electrolyte abnormalities.

Manage congestive heart failure if present (see Chapters 3.8).

Provide external warming if hypothermia persists after rehydration.

Identify and manage underlying disease(s).

Provide nutritional support if anorexia persists.

Further diagnostic testing

Complete cardiac evaluation, including echocardiogram Other tests as indicated (based on initial findings and cardiac exam) to rule out predisposing conditions

Prevention of extension of existing clot and new thromboembolic events

Antiplatelet therapy

#### • Áspirin

- Dog: 0.5 mg/kg by mouth q12h
- Cat: 81 mg/cat by mouth 2-3 times a week; low-dose, 5 mg/cat q72h (see text)

#### Clopidogrel

- Dog: 2-4 mg/kg by mouth q24h (dose not well-established)
- Cat: 18.75 mg/cat by mouth q24h (dose not wellestablished)

### Anticoagulant therapy

#### Sodium heparin

- Dog: 200-250 IU/kg administered intravenously, followed by 200-300 IU/kg administered subcutaneously q6-8h for 2-4 days or as needed
- Cat: same

#### Dalteparin sodium

- Dog: same as cat? (see text)
- Cat: 150 U/kg administered subcutaneously q4h? (see text)

#### • Enoxaparin

- Dog: same as cat?
- Cat: 1.5 mg/kg administered subcutaneously q6h? (see text)

Thrombolytic therapy (pursue only with caution, see text)

#### Streptokinase

- Dog: 90,000 IU infused intravenously over 20 to 30 minutes, then at 45,000 IU/h for 3 (or more) hours (see text)
- Cat: same

#### rt-PA

- Dog: 1 mg/kg bolus IV q1h for 10 doses (see text)
- Cat: 0.25-1 mg/kg/h (up to a total of 1-10 mg/kg) administered intravenously (see text)

 $\beta$ -blocking effect may contribute to peripheral vasoconstriction from unopposed  $\alpha$ -receptors, and the drug has no antithrombotic effects at clinical doses.

An analgesic is recommended, especially for the first 24 to 36 hours, because this is a painful condition. Butorphanol (0.15 to 0.5 mg/kg, administered intramuscularly into the cranial lumbar area or subcutaneously q1-3h) has been recommended, especially for the first 24 to 36 hours after the embolic event. Low-dose morphine (0.1 to 0.3 mg/kg q3-6h, administered intramuscularly or subcutaneously) could be considered, but some cats experience dysphoria. A fentanyl patch (25 µg/h size) applied to a shaved area of skin could

be used to help alleviate pain for up to 3 days, but because it takes about 12 hours to become effective, another analgesic is used simultaneously during this initial period. Respiratory depression and reduced gastrointestinal (GI) motility are potential side effects.

Acepromazine is not recommended for animals with arterial TE disease, despite its α-adrenergic receptor–blocking effects. Improved collateral flow has not been documented, and hypotension and exacerbation of dynamic ventricular outflow obstruction (in cats with hypertrophic obstructive cardiomyopathy) are potential adverse effects. Other supportive care is given to improve and maintain adequate

tissue perfusion, minimize further endothelial damage and blood stasis, and optimize organ function as well as to allow time for collateral circulation development.

Antiplatelet and anticoagulant therapies are used to reduce platelet aggregation and growth of existing thrombi. Although fibrinolytic therapy is used in some cases, dosage uncertainties, the need for intensive care, and the potential for serious complications stemming from reperfusion injury limit its use.

Aspirin (acetylsalicylic acid) is used commonly to block platelet activation and aggregation in patients with, or at risk for, TE disease. Aspirin irreversibly inhibits cyclooxygenase, which reduces prostaglandin and thromboxane A2 synthesis and therefore subsequent platelet aggregation, serotonin release, and vasoconstriction. Because platelets cannot synthesize additional cyclooxygenase, this reduction of procoagulant prostaglandins and thromboxane persists for the platelet's life span (7 to 10 days). Endothelial production of prostacyclin (also via the cyclooxygenase pathway) is reduced by aspirin but only transiently as endothelial cells synthesize additional cyclooxygenase. Aspirin's benefit may relate more to in situ thrombus formation; efficacy in acute arterial thromboembolism is unknown. Adverse effects of aspirin tend to be mild and uncommon, but the optimal dose is unclear. Cats lack an enzyme (glucuronyl transferase) that is needed to metabolize aspirin, so less frequent dosing is required compared with dogs. In cats with experimental aortic thrombosis, 10 to 25 mg/kg (1.25 grains/cat) given by mouth once every (2 to) 3 days inhibited platelet aggregation and improved collateral circulation. However, low-dose aspirin (5 mg/cat q72h) has also been used with fewer GI adverse effects, although its efficacy in preventing TE events is unknown. Aspirin therapy is started when the patient is able to take food and oral medications.

Other antiplatelet drugs are being studied. The thienopyridines inhibit adenosine diphosphate (ADP)-binding at platelet receptors and subsequent ADP-mediated platelet aggregation. Clopidogrel (Plavix; 18.75 mg/cat PO q24h) appears to have significant antiplatelet effects; daily dosing may be possible.

Heparin is indicated to limit extension of existing thrombi and prevent further TE episodes; it does not promote thrombolysis. Unfractionated heparin and a number of low-molecular-weight heparin (LMWH) products are available. Heparin's main anticoagulant effect is produced through AT activation, which in turn inhibits factors IX, X, XI, and XII and thrombin. Unfractionated heparin binds thrombin as well as AT. Heparin also stimulates release of tissue factor inhibitors from vascular sites, which helps reduce (extrinsic) coagulation cascade activation. Optimal dosing protocols for animals are not known. Unfractionated heparin is usually given as an initial intravenous (IV) bolus followed by subcutaneous (SC) injections (see Box 12-3). Heparin is not given IM because of the risk for hemorrhage at the injection site. Heparin doses (from 75 to 500 U/kg) have been used with uncertain efficacy. An initial IV dose of 200 IU/kg, followed by 150 to 200 IU/kg administered subcutaneously q6-8h for 2 to 4 days is one protocol. Monitoring the patient's activated partial thromboplastin time (aPTT) is recommended, although results may not accurately predict serum heparin concentrations. Pretreatment coagulation testing is done for comparison, and the goal is to prolong the aPTT to 1.5 to 2.5 times baseline. Activated clotting time is not recommended to monitor heparin therapy. Hemorrhage is the major complication. Protamine sulfate can be used to counteract heparin-induced bleeding. However, an overdose of protamine can paradoxically cause irreversible hemorrhage. Dosage guidelines for protamine sulfate are as follows: 1 mg/100 U of heparin is given if the heparin was given within the previous 60 minutes; 0.5 mg/100 U of heparin is given if the heparin was given more than 1 but less than 2 hours earlier; and 0.25 mg/100 U of heparin is given if more than 2 hours have elapsed since heparin was administered. Fresh frozen plasma may be needed to replenish AT. Heparin treatment is continued until the patient is stable and has been on antiplatelet therapy for a few days.

LMWH is a safer alternative to unfractionated heparin. LMWH products are a diverse group of depolymerized heparin that vary in size, structure, and pharmacokinetics. Their smaller size prevents simultaneous binding to thrombin and AT. LMWH products have more effect against factor Xa through their inactivation of AT. Because they have minimal ability to inhibit thrombin, they are less likely to cause bleeding. LMWH products have greater bioavailability and a longer half-life than unfractionated heparin when given subcutaneously because of lesser binding to plasma proteins as well as endothelial cells and macrophages. However, LMWH products do not markedly affect coagulation times, so monitoring aPTT is generally not necessary. LMWH effect can be monitored indirectly by anti-Xa activity. Optimal anti-Xa activity level in cats is not known; the target range in people is reported as 0.5 to 1.0 U/ml, although 0.3 to 0.6 U/ml has also been used. The LMWH products have differences in biological and clinical effects and are not interchangeable. The most effective dosage for the various LMWH products is not clearly established in dogs and cats. Commonly used dosages of dalteparin sodium (Fragmin; 100-150 U/kg administereed subcutaneously q8-24h) and enoxaparin (Lovenox; 1 mg/kg administered subcutaneously q12-24h) were extrapolated from human use. However, according to a recent study (Alwood et al., 2007), these doses do not produce a (human) target level of anti-Xa activity in cats. Although enoxaparin produced anti-Xa activity close to this level at 4 hours postdose, activity was undetectable 8 hours later. On the basis of this study, the predicted optimal dose and dosing interval to maintain anti-Xa activity within the (human) therapeutic range in normal cats are as follows: dalteparin, 150 U/kg administered subcutaneously q4h; and enoxaparin, 1.5 mg/kg administered subcutaneously q6h. The optimal therapeutic range in cats as well as the most effective dosage in sick cats are not yet known.

Drugs used to promote clot lysis include streptokinase and human recombinant tissue plasminogen activator (rt-PA). These agents increase conversion of plasminogen to plasmin to facilitate fibrinolysis. Veterinary experience with these agents is quite limited. Although they effectively break down clots, complications related to reperfusion injury and hemorrhage, the high mortality rate, the cost of therapy, the intensive care required, and the lack of clearly established dosing protocols have prevented their widespread use. Furthermore, a clear survival advantage has not been shown. If used, this therapy is best instituted within 3 to 4 hours of vascular occlusion. An intensive care setting, including continuous serum potassium concentration (or electrocardiographic [ECG]) monitoring to detect reperfusion-induced hyperkalemia, is recommended.

Streptokinase is a nonspecific plasminogen activator that promotes the breakdown of fibrin as well as fibrinogen. This action leads to the degradation of fibrin within thrombi and clot lysis but also potentially leads to systemic fibrinolysis, coagulopathy, and bleeding. Streptokinase also degrades factors V, VIII, and prothrombin. Although its half-life is about 30 minutes, fibrinogen depletion continues for much longer. Streptokinase has been used with variable success in a small number of dogs with arterial TE disease. The reported protocol is 90,000 IU of IV streptokinase infused over 20 to 30 minutes, then at a rate of 45,000 IU/hour for 3 (to 8) hours. Dilution of 250,000 IU into 5 ml saline, then into 50 ml to yield 5000 U/ml for infusion with a syringe pump has been suggested for cats. Adverse effects are minor in some cases, and bleeding may respond to discontinuing streptokinase. However, there is a risk for serious hemorrhage, and the mortality rate in clinical cases is high. Acute hyperkalemia (secondary to thrombolysis and reperfusion injury), metabolic acidosis, bleeding, and other complications are thought to be responsible for causing death. Streptokinase can increase platelet aggregability and induce platelet dysfunction. It is unclear if lower doses would be effective with fewer complications. Streptokinase combined with heparin therapy can increase the risk of hemorrhage, especially when coagulation times are increased. Streptokinase is potentially antigenic because it is produced by βhemolytic streptococci. No survival benefit has been shown for streptokinase therapy compared with conventional (i.e., aspirin and heparin) treatment in cats.

rt-PA is a single-chain polypeptide serine protease with a higher specificity for fibrin within thrombi and a low affinity for circulating plasminogen. Although the risk of hemorrhage is less than with streptokinase, there is the potential for serious bleeding as well as other side effects. rt-PA is also potentially antigenic in animals because it is a human protein. Like streptokinase, rt-PA induces platelet dysfunction but not hyperaggregability. Experience with rt-PA is very limited, and the optimal dosage is not known. An IV dose of 0.25 to 1 mg/kg/h up to a total of 1 to 10 mg/kg was used in a small number of cats; although signs of reperfusion occurred, the mortality rate was high. The cause of death in most cats was attributed to reperfusion (hyperkalemia, metabolic acidosis) and hemorrhage, although CHF and arrhythmias were also involved.

Surgical clot removal is generally not advised in cats. The surgical risk is high, and significant neuromuscular ischemic injury is likely to have already occurred by the time of surgery. Clot removal using an embolectomy catheter has not been very effective in cats.

In general, the prognosis is poor in cats with arterial TE disease. Historically, only a third of cats survive the initial episode. However, survival statistics improve when cats euthanized without therapy are excluded or when only cases from recent years are analyzed. Survival is better if only one limb is involved and/or if some motor function is preserved at presentation. Hypothermia and CHF at presentation are both associated with poor survival in cats. Other negative factors may include hyperphosphatemia, progressive hyperkalemia or azotemia, progressive limb injury (continued muscle contracture after 2 to 3 days, necrosis), severe LA enlargement, presence of intracardiac thrombi or spontaneous contrast ("swirling smoke") on echocardiogram, DIC, and history of thromboembolism.

Barring complications, limb function should begin to return within 1 to 2 weeks. Some cats become clinically normal within 1 to 2 months, although residual deficits may persist for a variable time. Tissue necrosis may require wound management and skin grafting. Permanent limb deformity develops in some cats, and amputation is occasionally necessary. Repeated events are common. Significant embolization of the kidneys, intestines, or other organs carries a grave prognosis.

# PROPHYLAXIS AGAINST ARTERIAL THROMBOEMBOLISM

Prophylactic therapy with an antiplatelet or anticoagulant drug is commonly used in animals thought to be at increased risk for TE disease. These include cats with cardiomyopathy (especially those with marked LA enlargement, echocardiographic evidence for intracardiac spontaneous contrast or thrombus, or a previous TE event) and animals with sepsis, IMHA, severe pancreatitis, or other procoagulant conditions. However, the efficacy of TE prophylaxis is unknown, and a strategy that consistently prevents thromboembolism is not yet identified.

Drugs used for arterial TE prophylaxis include aspirin, clopidogrel, warfarin (coumadin), and LMWH. Aspirin and clopidogrel present a low risk for serious hemorrhage and require less monitoring compared with warfarin. Adverse GI effects (e.g., vomiting, inappetence, ulceration, hematemesis) occur in some animals. Buffered aspirin formulation or an aspirin-Maalox combination product may be helpful. Low-dose aspirin (5 mg/cat every third day) has been advocated in cats. Although adverse effects are unlikely with this dose, it is not known whether antiplatelet effectiveness is compromised. Warfarin (discussed in more detail later) is associated with greater expense and a higher rate of fatal hemorrhage. No survival benefit has been shown for warfarin compared with aspirin in cats. In some reports, recurrent thromboembolism occurred in almost half of cats treated with warfarin. Clopidogrel or

LMWH prophylaxis may be more efficacious, with less risk of hemorrhage, but more experience with this therapy is needed. Recurrent TE events occurred in 20% of cats in one study (Smith, 2004). LMWH is expensive and must be given by daily SC injection, but some owners are motivated to do this. In cats without thrombocytopenia, aspirin may be used concurrently. Diltiazem, at clinical doses, does not appear to have significant platelet-inhibiting effects.

Warfarin inhibits the enzyme (vitamin K epoxide reductase) responsible for activating the vitamin K-dependent factors (II, VII, IX, and X), as well as proteins C and S. Initial warfarin treatment causes transient hypercoagulability because anticoagulant proteins have a shorter half-life than most procoagulant factors. Therefore heparin (e.g., 100 IU/ kg administered subcutaneously q8h) is given for 2 to 4 days after warfarin is initiated. There is wide variability in dose response and potential for serious bleeding, even in cats that are monitored closely. Warfarin is highly protein-bound; concurrent use of other protein-bound drugs or change in serum protein concentration can markedly alter the anticoagulant effect. Bleeding may be manifested as weakness, lethargy, or pallor rather than overt hemorrhage. A baseline coagulation profile and platelet count are obtained, and aspirin discontinued, before beginning treatment. The usual initial warfarin dose is 0.25 to 0.5 mg (total dose) administered orally q24-48h in cats. Uneven distribution of drug within the tablets is reported, so compounding rather than administering tablet fragments is recommended. Drug administration and blood sampling times should be consistent.

The dose is adjusted either on the basis of prothrombin time (PT) or the international normalization ratio (INR). The INR is a more precise method that has been recommended to prevent problems related to variation in commercial PT assays. The INR is calculated by dividing the animal's PT by the control PT and raising the quotient to the power of the international sensitivity index (ISI) of the thromboplastin used in the assay, or INR = (animal PT/ control PT) ISI. The ISI is provided with each batch of thromboplastin made. Extrapolation from human data suggests that an INR of 2 to 3 is as effective as higher values, with less chance for bleeding. Using a warfarin dose of 0.05 to 0.1 mg/kg/day in the dog achieves this INR in about 5 to 7 days. Heparin overlap until the INR is >2 is recommended. When PT is used to monitor warfarin therapy, a goal of 1.25 to 1.5 (to 2) times pretreatment PT at 8 to 10 hours after dosing is advised; the animal is weaned off heparin when the INR is >1.25. The PT is evaluated (several hours after dosing) daily initially, then at progressively increasing time intervals (e.g., twice a week, then once a week, then every month to 2 months) as long as the cat's condition appears stable.

If the PT or INR increases excessively, warfarin is discontinued and vitamin  $K_1$  administered (1 to 2 mg/kg/day administered orally or subcutaneously) until the PT is normal and the packed cell volume (PCV) is stable. Transfu-

sion with fresh frozen plasma, packed red blood cells, or whole fresh blood is sometimes necessary.

# SYSTEMIC ARTERIAL THROMBOEMBOLISM IN DOGS

Arterial TE disease in dogs is relatively uncommon compared with cats. Nevertheless, it has been associated with many conditions, including protein-losing nephropathies, hyperadrenocorticism, neoplasia, chronic interstitial nephritis, HWD, hypothyroidism, gastric dilatation-volvulus, pancreatitis, and several cardiovascular diseases. Kidney disease was present in about half of the dogs with TE disease in one report (Van Winkle, 1993). Vegetative endocarditis is the most common cardiac disease associated with systemic thromboembolism. Other cardiovascular conditions that have been associated with canine TE disease include patent ductus arteriosus (surgical ligation site), dilated cardiomyopathy, myocardial infarction, arteritis, aortic intimal fibrosis, atherosclerosis, aortic dissection, granulomatous inflammatory erosion into the left atrium, and other thrombi in the left heart. TE disease is a rare complication of arteriovenous (A-V) fistulae; it may relate to venous stasis from distal venous hypertension. Aortic TE has occurred in Greyhounds without overt underlying abnormalities as well as in those with protein-losing nephropathy or intramuscular hemangiosarcoma in the thigh muscles. Affected dogs typically present for intermittent rear limb lameness (claudication) and have weak femoral pulses on the affected side, and the thrombi are obvious during abdominal ultrasonography.

Atherosclerosis is uncommon in dogs, but it has been associated with TE disease in this species, as it has in people. Endothelial disruption in areas of atherosclerotic plaque, hypercholesterolemia, increased PAJ-1, and possibly other mechanisms may be involved in thrombus formation. Atherosclerosis may develop with profound hypothyroidism, hypercholesterolemia, or hyperlipidemia. The aorta as well as coronary and other medium to large arteries are affected. Myocardial and cerebral infarctions occur in some cases, and there is a high rate of interstitial myocardial fibrosis in affected dogs.

Vasculitis related to infectious, inflammatory, immunemediated, or toxic disease occasionally underlies TE events. Arteritis of immune-mediated pathogenesis is described in some young Beagles and other dogs. Inflammation and necrosis that affect small to medium-sized arteries may be associated with thrombosis.

Coronary artery thromboembolism causes myocardial ischemia and infarction. Infective endocarditis, neoplasia that involves the heart directly or by neoplastic emboli, coronary atherosclerosis, dilated cardiomyopathy, degenerative mitral valve disease with CHF, and coronary vasculitis are reported causes. In other dogs coronary TE events have occurred with severe renal disease, IMHA, exogenous corticosteroids or hyperadrenocorticism, and acute pancreatic

necrosis. These cases may have TE lesions in other locations as well.

#### **Clinical Features**

There appear to be no age, breed, or sex predilections for arterial TE disease in dogs. As in cats, the distal aorta is the most common location for clinically recognized thromboemboli. In contrast to cats, most dogs have some clinical signs from 1 to 8 weeks before presentation. Less than a quarter of cases have peracute paralysis without prior signs of lameness, as usually occurs in cats. Signs related to the TE event include pain, hindlimb paresis, lameness or weakness (which may be progressive or intermittent), and chewing or hypersensitivity of the affected limb(s) or lumbar area. Although about half of affected dogs present with sudden paralysis, this is often preceded by a variable period of lameness. Intermittent claudication, common in people with peripheral occlusive vascular disease, may be a manifestation of distal aortic TE disease. This involves pain, weakness, and lameness that develop during exercise. These signs intensify until walking becomes impossible, then disappear with rest. Inadequate perfusion during exercise leads to lactic acid accumulation and cramping.

Physical examination findings in dogs with aortic thromboembolism are similar to those in cats, including absent or weak femoral pulses, cool extremities, hindlimb pain, loss of sensation in the digits, hyperesthesia, cyanotic nailbeds, and neuromuscular dysfunction. Occasionally, a brachial or other artery is embolized. TE disease involving an abdominal organ causes abdominal pain, with clinical and laboratory evidence of damage to the affected organ.

Coronary artery thromboembolism is likely to be associated with arrhythmias, as well as ST segment and T wave changes on ECG. Ventricular (or other) tachyarrhythmias are common, but if the atrioventricular (AV) nodal area is injured, conduction block may result. Clinical signs of acute myocardial infarction/necrosis may mimic those of pulmonary TE disease; these include weakness, dyspnea, and collapse. Respiratory difficulty may develop as a result of pulmonary abnormalities or left heart failure (pulmonary edema) depending on the underlying disease and degree of myocardial dysfunction. Some animals with respiratory distress have no radiographically evident pulmonary infiltrates. Increased pulmonary venous pressure preceding overt edema (from acute myocardial dysfunction) or concurrent pulmonary emboli are potential causes. Other findings in animals with myocardial necrosis include sudden death, tachycardia, weak pulses, increased lung sounds or crackles, cough, cardiac murmur, hyperthermia or sometimes hypothermia, and (less commonly) GI signs. Signs of other systemic disease may be concurrent. Acute ischemic myocardial injury that causes sudden death may not be detectable on routine histopathology.

## Diagnosis

Thoracic radiography is used to screen for cardiac abnormalities, especially in animals with systemic arterial TE

disease and for pulmonary changes in animals suspected to have pulmonary thromboemboli. Evidence for CHF or other pulmonary disease associated with TE disease (e.g., neoplasia, HWD, other infections) may also be found.

A complete echocardiographic exam is important to define whether (and what type of) heart disease might be present. Thrombi within the left or right heart chambers and proximal great vessels can be readily seen with two-dimensional echocardiography. In dogs with coronary TE disease, the echocardiographic examination may indicate reduced myocardial contractility with or without regional dysfunction. Areas of myocardial fibrosis secondary to chronic ischemia or infarction appear hyperechoic compared with the surrounding myocardium. Thromboemboli in the distal aorta (or other vessel) may be visible by ultrasonography as well. Doppler studies can demonstrate partial or complete obstruction to blood flow in some cases.

Angiography may be used to document vascular occlusion when ultrasonography is inconclusive or unavailable. It also can show the extent of collateral circulation. The choice of selective or nonselective technique depends on patient size and the suspected location of the clot.

Routine laboratory test results depend largely on the disease process underlying the TE event(s). Systemic arterial TE disease also produces elevated muscle enzyme concentrations from skeletal muscle ischemia and necrosis. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities rise soon after the TE event. Widespread muscle injury causes increased lactate dehydrogenase and creatine kinase (CK) activities as well.

Coagulation test results in patients with TE disease are variable. The concentration of FDPs or p-dimer may be increased, but this can occur in patients with inflammatory disease and is not specific for a TE event or DIC. Modestly increased p-dimer concentrations occur in diseases such as neoplasia, liver disease, and IMHA. This could reflect subclinical TE disease or another clot activation mechanism because these conditions are associated with a procoagulant state. Body cavity hemorrhage also causes a rise in D-dimer concentrations. Because this condition is associated with increased fibrin formation, elevated p-dimer levels may not indicate TE disease in such cases. The specificity of p-dimer testing for pathologic thromboembolism is lower at lower p-dimer concentrations, but the high sensitivity at lower concentrations provides an important screening tool. Ddimer testing appears to be as specific for DIC as FDP measurement. A number of assays have been developed to measure p-dimer concentrations in dogs; some are qualitative or semiquantitative (i.e., latex agglutination, immunochromatographic, and immunofiltration tests), others are more quantitative (i.e., immunoturbidity, enzymatic immunoassays). It is important to interpret p-dimer results in the context of other clinical and test findings. Assays for circulating AT and proteins C and S are also available for dogs and cats. Deficiencies of these proteins are associated with increased risk of thrombosis.

Thromboelastography (TEG) provides an easy point-ofcare method of assessing global hemostasis and is quite valuable when evaluating patients with TE disease.

# **Treatment and Prognosis**

The goals of therapy are the same as for cats with TE disease: Stabilize the patient by supportive treatment as indicated, prevent extension of the existing thrombus and additional TE events, and reduce the size of the thromboembolus and restore perfusion. Supportive care is given to improve and maintain adequate tissue perfusion, minimize further endothelial damage and blood stasis, and optimize organ function as well as to allow time for collateral circulation development. Correcting or managing underlying disease(s), to the extent possible, is also important. Antiplatelet and anticoagulant therapies are used to reduce platelet aggregation and growth of existing thrombi as in cats (see p. 199). The results of the TEG, if available, should be used to monitor response to anticoagulants in patients with TE disease.

Management strategies used for TE disease are outlined in Box 12-3. Although fibrinolytic therapy is used in some cases, dosage uncertainties, the need for intensive care, and the potential for serious complications limit its use. The reported streptokinase protocol for dogs is 90,000 IU infused intravenously over 20 to 30 minutes, then continued at a rate of 45,000 IU/hour for 3 (to 12) hours. In dogs, rt-PA has been used as 1 mg/kg boluses administered intravenously q1h for 10 doses, with IV fluid, other supportive therapy, and close monitoring. The half-life of t-PA is about 2 to 3 minutes in dogs, but effects persist longer because of binding to fibrin. The consequences of reperfusion injury present serious complications to thrombolytic therapy. The iron chelator deferoxamine mesylate has been used in an attempt to reduce oxidative damage caused by free radicals involving iron. Allopurinol also has been used but with uncertain results. Clot removal using an embolectomy catheter has not been very effective in cats but might be more successful in dogs of larger size.

Fluid therapy is used to expand vascular volume, support blood pressure, and correct electrolyte and acid/base abnormalities depending on individual patient needs. However, for animals with heart disease and especially CHF, fluid therapy is given only with great caution (if at all). Hypothermia that persists after circulating volume is restored can be addressed with external warming. Specific treatment for heart disease, CHF, and arrhythmias is provided as indicated (see Chapters 3 and 4 and other relevant chapters). Acute respiratory signs may signal CHF, pain, or pulmonary thromboembolism. Differentiation is important because diuretic or vasodilator therapy could worsen perfusion in animals without CHF.

Because acute arterial embolization is particularly painful, analysesic therapy is important in such cases, especially for the first 24 to 36 hours (see Box 12-3). Loosely bandaging the affected limb(s) to prevent self-mutilation may be needed in some animals with aortic TE disease. Renal function and

serum electrolyte concentrations are monitored daily or more frequently if fibrinolytic therapy is used. Continuous ECG monitoring during the first several days can help the clinician detect acute hyperkalemia associated with reperfusion (see Chapter 2, p. 31). In general, the prognosis is poor.

# PROPHYLAXIS AGAINST ARTERIAL THROMBOEMBOLISM

Prophylactic strategies are the same as for cats. Aspirin, LMWH, warfarin, or possibly clopidogrel are agents to consider. If warfarin is used, the usual initial warfarin dose is 0.25 to 0.5 mg (total dose) administered orally q24(to 48)h in cats; 0.1 to 0.2 mg/kg administered orally q24h in dogs. A loading dose of ~0.2 mg/kg for 2 days appears to be safe in dogs.

#### **VENOUS THROMBOSIS**

Thrombosis in large veins is more likely to be clinically evident than thrombosis in small vessels. Cranial vena caval thrombosis has been associated with IMHA and/or immunemediated thrombocytopenia, sepsis, neoplasia, proteinlosing nephropathies, mycotic disease, heart disease, and glucocorticoid therapy (especially in patients with systemic inflammatory disease) in dogs. Most cases have more than one predisposing factor. An indwelling jugular catheter increases the risk for cranial caval thrombosis, probably by causing vascular endothelial damage or laminar flow disruption or by acting as a nidus for clot formation.

Portal vein thrombosis, along with DIC, has occurred in dogs with pancreatitis and pancreatic necrosis. Peritonitis, neoplasia, hepatitis, protein-losing nephropathy, IMHA, and vasculitis have also been diagnosed occasionally in dogs with portal thrombosis. A high proportion of dogs with incidental portal or splenic vein thrombosis are receiving corticosteroids.

Systemic venous thrombosis produces signs related to increased venous pressure upstream from the obstruction. Thrombosis of the cranial vena cava can lead to the cranial caval syndrome. The cranial caval syndrome is characterized by bilaterally symmetric subcutaneous edema of the head, neck, and forelimbs; another cause of this syndrome is external compression of the cranial cava, usually by a neoplastic mass. Pleural effusion occurs commonly. This effusion is often chylous because lymph flow from the thoracic duct into the cranial vena cava is also impaired. Palpable thrombosis extends into the jugular veins in some cases. Because vena caval obstruction reduces pulmonary blood flow and left heart filling, signs of poor cardiac output are common.

Vena caval thrombosis may be visible on ultrasound exam, especially when the clot extends into the right atrium. Portal vein thrombosis and thromboemboli in the aorta or other large peripheral vessels can also be documented on ultrasound examination.

Clinicopathic findings generally reflect underlying disease as well as tissue damage resulting from vascular obstruction.

Cranial caval thrombosis has been associated with thrombocytopenia.

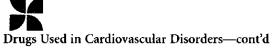
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# Drugs Used in Cardiovascular Disorders

TRADE NAME	DOG	CAT
Lasix Salix	1 to 3 mg/kg q8-24h chronic PO (use lowest effective dose); or (acute therapy) 2 to 5 mg/kg q1-4h until RR decreases, then 1 to 4 mg/kg q6-12h IV, IM, SC; or 0.6 to 1 mg/kg/hr CRI (see Chapter 3)	1 to 2 mg/kg q8-12h chronic PO (use lowest effective dose); or (acute therapy) up to 4 mg/kg q1-4h until RR decreases, then q6-12h IV, IM, SC as needed
Aldactone	0.5 to 2 mg/kg q(12h-)24h PO	0.5 to 1 mg/kg q(12-)24h PO
Diuril Hydrodiuril	20 to 40 mg/kg q12h PO 1 to 4 mg/kg q12h PO	Same 1 to 2 mg/kg q12h PO
	Lasix Salix Aldactone Diuril	Lasix Salix 1 to 3 mg/kg q8-24h chronic PO {use lowest effective dose}; or {acute therapy} 2 to 5 mg/kg q1-4h until RR decreases, then 1 to 4 mg/kg q6-12h IV, IM, SC; or 0.6 to 1 mg/kg/hr CRI {see Chapter 3}  Aldactone Diuril  O.5 to 2 mg/kg q(12h-)24h PO 20 to 40 mg/kg q12h PO



GENERIC NAME	TRADE NAME	DOG	CAT
Angiotensin Converti	ng Enzyme Inhibit	ors	
Enalapril	Enacard Vasotec	0.5 mg/kg q(12-)24h PO; or for hypertensive crisis: enalaprilat 0.2 mg/kg IV, repeat q1-2h as needed	0.25 to 0.5 mg/kg q(12-)24h PO
Benazepril Captopril	Lotensin Capoten	0.25 to 0.5 mg/kg q24(-12)h PO 0.5 to 2 mg/kg q8-12h PO (0.25 to 0.5 mg/kg initial dose)	Same 0.5 to 1.25 mg/kg q12-24h PO
Lisinopril	Prinivil Zestril	0.25 to 0.5 mg/kg q24(-12)h PO	0.25-0.5 mg/kg q24h PO
Fosinopril	Monopril	0.25-0.5 mg/kg q24h PO	
Ramipril	Altace	0.125 to 0.25 mg/kg q24hr PO	_
lmidapril	Tanatril, Prilium	0.25 mg/kg q24hr PO	_
Other Vasodilators			
Hydralazine	Apresoline	0.5 to 2 mg/kg q12h PO (to 1 mg/kg initial) For decompensated CHF: 0.5 to 1 mg/kg PO, repeat in 2-3h, then q12h (see Chapter 3); or (for hypertensive crisis) 0.2 mg/kg IV	2.5 (up to 10) mg per cat q12h PO
Amlodipine besylate	Norvasc	0.05 to 0.3 (-0.5) mg/kg q(12-)24h PO	0.3125-0.625 mg/cat q24(-12-)hr PO
Prazosin	Minipress	Small dogs (<5 kg): do not use; medium dogs: 1 mg q8-12h PO; large dogs: 2 mg q8h PO (or 0.05 to 0.2 mg/kg q8-12h PO)	Do not use
Na⁺ nitroprusside	Nitropress	0.5 to 1 μg/kg/min CRI (initial), to 5 to 15 μg/kg/min CRI	Same
Nitroglycerine ointment 2%	Nitrobid Nitrol	<sup>1</sup> / <sub>2</sub> to 1 <sup>1</sup> / <sub>2</sub> inch q4-6h cutaneously	$^{1}/_{4}$ to $^{1}/_{2}$ inch q4-6h cutaneously
Isosorbide dinitrate	lsordil Titradose	0.5 to 2 mg/kg q8(-12)h PO	_
Phenoxybenzamine Phentolamine	Dibenzyline Regitine	0.2 (to 1.5) mg q(8-)12h PO 0.02 to 0.1 mg/kg IV bolus, followed by CRI to effect	0.2 to 0.5 mg/kg q12h PO Same
Acepromazine		0.05 to 0.1 mg/kg (up to 3 mg total) IV	Same
Positive Inotropic Dru	gs		
Pimobendan Digoxin	Vetmedin Cardoxin Digitek Lanoxin	0.1 to 0.3 mg/kg q12h PO Oral: dogs <22 kg, 0.005 to 0.008 mg/kg q12h; dogs >22 kg, 0.22 mg/m² or 0.003 to 0.005 mg/kg q12h. Decrease by 10% for elixir. Maximum 0.5 mg/day (0.375 mg/day for Doberman Pinchers) IV loading: 0.01 to 0.02 mg/kg; give ¹/₄ of total dose in slow boluses over 2 to 4h to effect	Same Oral: 0.007 mg/kg q48h IV loading: 0.005 mg/kg—give 1/2 of total, then 1 to 2h later give 1/4 dose bolus as needed
Dobutamine	Dobutrex	1 to 10 μg/kg/min CRI (start low)	Same
Dopamine	Intropin	1 to 10 μg/kg/min CRI (start low)	1 to 5 μg/kg/min CRI (start low)
Amrinone	Inocor	1 to 3 mg/kg initial bolus, IV; 10 to 100 μg/kg/min CRI	Same?
Milrinone	Primacor	50 μg/kg IV over 10 min initially; 0.375 to 0.75 μg/kg/min CRI (humans)	Same?



GENERIC NAME	TRADE NAME	DOG	CAT
Antiarrhythmic Drugs Class I			
Lidocaine	Xylocaine	Initial boluses of 2 mg/kg slowly IV, up to 8 mg/kg; or rapid IV infusion at 0.8 mg/kg/min; if effective, then 25 to 80 µg/kg/min CRI	Initial bolus of 0.25 to 0.5 (or 1.0) mg/kg slowly IV; can repeat boluses of 0.15–0.25 mg/kg, up to total of 4 mg/kg; if effective, 10–40 mcg/kg/minute CRI
Procainamide	Pronestyl Pronestyl SR Procan SR	6 to 10 (up to 20) mg/kg IV over 5 to 10 min; 10 to 50 μg/kg/min CRI; 6 to 20 (up to 30) mg/kg q4-6h IM; 10 to 25 mg/kg q6h PO (sustained release: q6-8h)	1 to 2 mg/kg slowly IV; 10 to 20 μg/kg/min CRI; 7.5 to 20 mg/kg q(6 to) 8h IM, PO
Quinidine	Quinidex Extentabs Quinaglute Dura-Tabs Cardioquin	6 to 20 mg/kg q6h IM (loading dose 14 to 20 mg/kg); 6 to 16 mg/kg q6h PO; sustained action preps 8 to 20 mg/kg q8h PO	6 to 16 mg/kg q8h IM, PO
Mexiletine	Mexitil Dilantin	10 mg/kg slovy IV: 30 to 50 mg/kg g8h PO	— Do not use
Phenytoin Propafenone	Rythmol	10 mg/kg slow IV; 30 to 50 mg/kg q8h PO Dog: (?) 3 to 4 mg/kg q8hr PO	—
Flecainide	Tambocor	Dog: (?) 1 to 5 mg/kg q8-12hr PO	_
Class II			
Atenolol Propranolol	Tenormin Inderal	<ul> <li>0.2 to 1 mg/kg q12-24h PO (start low)</li> <li>IV: initial bolus of 0.02 mg/kg slowly, up to max. of 0.1 mg/kg</li> <li>Oral: initial dose of 0.1 to 0.2 mg/kg q8h, up to max. of 1 mg/kg q8h</li> </ul>	6.25 to 12.5 mg per cat q(12-)24h PO IV: Same Oral: 2.5 up to 10 mg per cat q8- 12h
Esmolol	Brevibloc	0.1 to 0.5 mg/kg IV over 1 minute (loading dose), followed by infusion of 0.025 to 0.2 mg/kg/minute	Same
Metroprolol	Lopressor	0.2 mg/kg initial dose q8h PO; up to 1 mg/kg q8h	_
Class III			
Sotalol Amiodarone	Betapace Cordarone	1 to 3.5 (-5) mg/kg q12hr PO 10 mg/kg q12hr PO for 7 days, then 8 mg/kg q24hr PO (lower as well as higher doses have been used); 3 (to 5) mg/kg slowly (over 10–20 minutes) IV (can repeat but do not exceed 10 mg/kg in 1 hour)	
Class IV			
Diltiazem	Cardizem Cardizem-CD Dilacor XR	Oral maintenance: initial dose 0.5 mg/kg (up to 2+ mg/kg) q8hr PO; acute IV for supraventricular tachycardia: 0.15–0.25 mg/kg over 2–3 minutes IV, can repeat every 15 minutes until conversion or maximum 0.75 mg/kg; CRI: 5–15 mg/kg/hr; PO loading dose: 0.5 mg/kg PO followed by 0.25 mg/kg PO q1hr to a total of 1.5(-2.0) mg/kg or conversion. Diltiazem XR: 1.5 to 4 mg/kg q12-24h PO	Same? Far hypertrophic cardiomyapathy, 1 to 2.5 mg/kg q8h PO; sustained release Cardizem - CD: 10 mg/ kg/day; diltiazem XR: 30 mg/ cat/day, can increase to 60 mg/ day in some cats if necessary



GENERIC NAME	TRADE NAME	DOG	CAT
Verapamil	Calan Isoptin	0.02 to 0.05 mg/kg slowly IV; can repeat q5 min, up to total of 0.15 (to 0.2) mg/ kg; 0.5 to 2 mg/kg q8h PO	Initial dose 0.025 mg/kg slowly IV; can repeat q5 min, up to total of 0.15 (to 0.2) mg/kg; 0.5 to 1 mg/kg q8h PO
Antiarrhythmic Drug:	<b>s</b>		
Atropine		0.02 to 0.04 mg/kg IV, IM, SC; Atrophine challenge test: 0.04 mg/kg IV (see Chapter 4)	Same
Glycopyrrolate	Robinul	0.005 to 0.01 mg/kg IV, IM; 0.01 to 0.02 mg/kg SC	Same
Propantheline Br Hyoscyamine	Pro-Banthine Anaspaz, Levsin	3.73 to 7.5 mg q8-12h, PO 0.003-0.006 mg/kg q8hr PO	_ _
Sympathomimetics			
Isoproterenol Terbutaline	Isuprel Brethine Bricanyl	0.045 to 0.09 μg/kg/min CRI 2.5 to 5 mg per dog q8-12h PO	Same 1.25 mg per cat q12h PO
Drugs for Heartworn Heartworm Adulticid			
Melarsomine	Immiticide	Follow manufacturer's instructions carefully; standard regimen: 2.5 mg/kg deep into lumbar muscles q24h for 2 doses. Alternate regimen: 2.5 mg/kg IM for 1 dose; 1 month later give standard regimen	_
Microfilaricide Therap	oy (often not need	ded)	
lvermectin	lvomec Heartgard-30	One dose (0.05 mg/kg) orally 3 to 4 weeks after adulticide therapy. Can repeat in 2 weeks	Same
Milbemycin oxime	Interceptor	One dose of 0.5 to 1.0 mg/kg PO; can repeat in 2 weeks	Same
Heartworm Preventic	оп		
lvermectin Milbemycin oxime Selamectin Moxidectin Diethylcarbamazine	Heartgard-30 Interceptor Revolution ProHeart Filaribits Nemacide	0.006 to 0.012 mg/kg PO once a month 0.5 (to 1.0) mg/kg PO once a month 6 to 12 mg/kg topically once a month 0.003 mg/kg once a month 3 mg/kg (6.6 mg/kg of 50% citrate) PO once a day	0.024 mg/kg PO once a month 2 mg/kg PO once a month Same
Antithrombotic Agent	ts		
Aspirin		0.5 mg/kg q12h PO	81 mg/cat 2–3 times a week PO; low-dose, 5 mg/cat q72h (see Chapter 12)
Clopidogrel	Płavix	2–4 mg/kg q24h PO (dose not well established)	18.75 mg/cat q24h PO (dose not well established)
Heparin Na		200–250 IU/kg IV, followed by 200–300 IU/kg q6-8h SC for 2–4 days or as needed	Same
Dalteparin Na	Fragmin	100-150 U/kg q(12)-24h SC (see Chapter	100 U/kg q(12)-24h SC (see
Danepann 14a	ŭ	12)	Chapter 12)

PO, By mouth; IV, intravenous; IM, intramuscular; SC, subcutaneous; CHF, congestive heart failure; CRI, constant rate infusion; RR, respiratory rate.

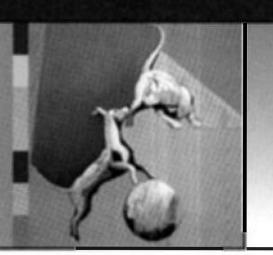
# PART TWO

# RESPIRATORY SYSTEM DISORDERS

Eleanor C. Hawkins

# CHAPTER

# Clinical Manifestations of Nasal Disease



# CHAPTER OUTLINE

GENERAL CONSIDERATIONS NASAL DISCHARGE SNEEZING

Reverse Sneezing STERTOR FACIAL DEFORMITY

#### GENERAL CONSIDERATIONS

The nasal cavity and paranasal sinuses have a complex anatomy and are lined by mucosa. Their rostral portion is inhabited by bacteria in health. Nasal disorders are frequently associated with mucosal edema, inflammation, and secondary bacterial infection. They are often focal or multifocal in distribution. These factors combine to make the accurate diagnosis of nasal disease a challenge that can be met only through a thorough, systematic approach.

Diseases of the nasal cavity and paranasal sinuses typically cause nasal discharge; sneezing; stertor (i.e., snoring or snorting sounds); facial deformity; systemic signs of illness (e.g., lethargy, inappetence, weight loss); or, in rare instances, central nervous system signs. The most common clinical manifestation is nasal discharge. The general diagnostic approach to animals with nasal disease is included in the discussion of nasal discharge. Specific considerations related to sneezing, stertor, and facial deformity follow. Stenotic nares are discussed in the section on brachycephalic airway syndrome (Chapter 18).

# NASAL DISCHARGE

# Classification and Etiology

Nasal discharge is most commonly associated with disease localized within the nasal cavity and paranasal sinuses,

although it may also develop with disorders of the lower respiratory tract, such as bacterial pneumonia and infectious tracheobronchitis, or systemic disorders, such as coagulopathies and systemic hypertension. Nasal discharge is characterized as serous, mucopurulent with or without hemorrhage, or purely hemorrhagic (epistaxis). Serous nasal discharge has a clear, watery consistency. Depending on the quantity and duration of the discharge, a serous discharge may be normal, may be indicative of viral upper respiratory infection, or may precede the development of a mucopurulent discharge. As such, many of the causes of mucopurulent discharge can initially cause serous discharge (Box 13-1).

Mucopurulent nasal discharge is typically characterized by a thick, ropey consistency and has a white, yellow, or green tint. A mucopurulent nasal discharge implies inflammation. Most intranasal diseases result in inflammation and secondary bacterial infection, making this sign a common presentation for most nasal diseases. Potential etiologies include infectious agents, foreign bodies, neoplasia, polyps, and extension of disease from the oral cavity (see Box 13-1). If mucopurulent discharge is present in conjunction with signs of lower respiratory tract disease, such as cough, respiratory distress, or auscultable crackles, the diagnostic emphasis is initially on evaluation of the lower airways and pulmonary parenchyma. Hemorrhage may be associated with mucopurulent exudate from any etiology, but significant and prolonged bleeding in association with mucopurulent discharge is usually associated with neoplasia or mycotic infections.

Persistent pure hemorrhage (epistaxis) can result from trauma, local aggressive disease processes (e.g., neoplasia, mycotic infections), systemic hypertension, or systemic bleeding disorders. Systemic hemostatic disorders that can cause epistaxis include thrombocytopenia, thrombocytopathies, von Willebrand's disease, rodenticide toxicity, and vasculitides. Ehrlichiosis and Rocky Mountain spotted fever can cause epistaxis through several of these mechanisms. Nasal foreign bodies may cause hemorrhage after entry into



Differential Diagnoses for Nasal Discharge in Dogs and Cats

#### Serous Discharge

Normal

Viral infection

Early sign of etiology of mucopurulent discharge

#### Mucopurulent Discharge With or Without Hemorrhage

Viral infection

Feline herpesvirus (rhinotracheitis virus)

Feline calicivirus

Canine influenza virus

Bacterial infection (usually secondary)

Fungal infection

**Aspergillus** 

Cryptococcus

Penicillium

Rhinosporidium

Nasal parasites

**Pneumonyssoides** 

Capillaria (Eucoleus)

Foreign body

Neoplasia

Carcinoma

Sarcoma

Malignant lymphoma

Nasopharyngeal polyp

Extension of oral disease

Tooth root abscess

Oronasal fistula

Deformed palate

Allergic rhinitis

Feline chronic rhinosinusitis

Canine chronic/lymphoplasmacytic rhinitis

## Pure Hemorrhagic Discharge (Epistaxis)

Nasal disease

Acute trauma

Acute foreign body

Neoplasia

Fungal infection

Less commonly, other etiologies as listed for mucopurulent discharge

Systemic disease

Clotting disorders

- Thrombocytopenia
- Thrombocytopathy
- Coagulation defect

Vasculitis

Hyperviscosity syndrome

Polycythemia

Systemic hypertension

the nasal cavity, but the bleeding tends to subside quickly. Bleeding can also occur after aggressive sneezing from any cause.

# Diagnostic Approach

A complete history and physical examination can be used to prioritize the differential diagnoses for each type of nasal discharge (see Box 13-1). Acute and chronic diseases are defined by obtaining historical information regarding the onset of signs and evaluating the overall condition of the animal. Acute processes, such as foreign bodies or acute feline viral infections, often result in a sudden onset of signs, including sneezing, and the animal's body condition is excellent. In chronic processes, such as mycotic infections or neoplasia, signs are present over a long period of time and the overall body condition can be deleteriously affected. A history of gagging or retching may indicate masses, foreign bodies, or exudate in the caudal nasopharynx.

Nasal discharge is characterized as unilateral or bilateral on the basis of both historical and physical examination findings. When nasal discharge is apparently unilateral, a cold microscope slide may be held close to the external nares to determine the patency of the side of the nasal cavity without discharge. Condensation will not be visible in front of the naris if airflow is obstructed, which suggests that the disease is actually bilateral. Although any bilateral process can cause signs from one side only and unilateral disease can progress to involve the opposite side, some generalizations can be made. Systemic disorders and infectious diseases tend to involve both sides of the nasal cavity, whereas foreign bodies, polyps, and tooth root abscessation tend to cause unilateral discharge. Neoplasia may initially cause unilateral discharge that later becomes bilateral after destruction of the nasal septum.

Ulceration of the nasal plane is highly suggestive of a diagnosis of nasal aspergillosis (Fig. 13-1). Polypoid masses protruding from the external nares in the dog are typical of rhinosporidiosis, and in the cat they are typical of cryptococcosis.

A thorough assessment of the head, including facial symmetry, teeth, gingiva, hard and soft palate, mandibular lymph nodes, and eyes, should be performed. Mass lesions invading beyond the nasal cavity can cause deformity of facial bones or the hard palate, exophthalmos, or inability to retropulse the eye. Pain on palpation of the nasal bones is suggestive of aspergillosis. Gingivitis, dental calculi, loose teeth, or pus in the gingival sulcus should raise an index of suspicion for oronasal fistulae or tooth root abscess, especially if unilateral nasal discharge is present. Foci of inflammation and folds of hyperplastic gingiva in the dorsum of the mouth should be probed for oronasal fistulae. A normal examination of the oral cavity does not rule out oronasal fistulae or tooth root abscess. The hard and soft palates are examined for deformation, erosions, or congenital defects such as clefts or hypoplasia. Mandibular lymph node enlargement suggests active inflammation or neoplasia, and fine-needle aspirates of enlarged or firm nodes are evaluated for organisms, such as



PIG 13-1
Depigmentation and ulceration of the planum nasale is suggestive of nasal aspergillosis. The visible lesions usually extend from one or both nares and are most severe ventrally. This dog has unilateral depigmentation and mild ulceration.

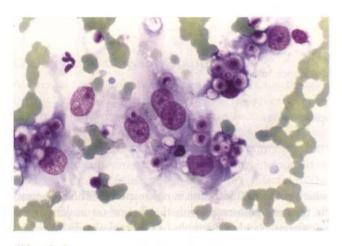


FIG 13-2

Photomicrograph of fine-needle aspirate of a cat with facial deformity. Identification of cryptococcal organisms provides a definitive diagnosis for cats with nasal discharge or facial deformity. Organisms can often be found in swabs of nasal discharge, fine-needle aspirates of facial masses, or fine-needle aspirates of enlarged mandibular lymph nodes. The organisms are variably sized, ranging from about 3 to 30  $\mu$ m in diameter, with a wide capsule and narrow-based budding. They may be found intracellularly or extracellularly.

Cryptococcus, and neoplastic cells (Fig. 13-2). A fundic examination should always be performed because active chorioretinitis can occur with cryptococcosis, ehrlichiosis, and malignant lymphoma (Fig. 13-3). Retinal detachment can occur with systemic hypertension or mass lesions extending into the bony orbit. With epistaxis, identification of petechiae or hemorrhage in other mucous membranes, skin, ocular fundus, feces, or urine supports a systemic bleeding disorder. Note that melena may be present as a result of swallowing blood from the nasal cavity.

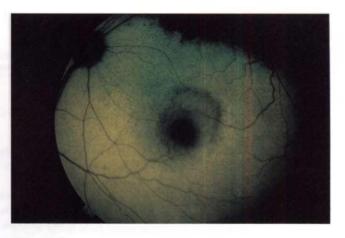


FIG 13-3
Fundic examination can provide useful information in animals with signs of respiratory tract disease. This fundus from a cat with chorioretinitis caused by cryptococcosis has a large, focal, hyporeflective lesion in the area centralis. Smaller regions of hyporeflectivity were also seen. The optic disk is in the upper left-hand corner of the photograph. (Courtesy M. Davidson, North Carolina State University,

Raleigh, N.C.)

Diagnostic tests that should be considered for a dog or cat with nasal discharge are included in Box 13-2. The signalment, history, and physical examination findings dictate in part which diagnostic tests are ultimately required to establish the diagnosis. As a general rule, less invasive diagnostic tests are performed initially. A complete blood count (CBC) with platelet count, coagulation panel (i.e., activated clotting time or prothrombin and partial thromboplastin times), buccal mucosal bleeding time, and arterial blood pressure should be evaluated in dogs and cats with epistaxis. Von Willebrand's factor assays are performed in purebred dogs with epistaxis and in dogs with prolonged mucosal bleeding times. Determination of Ehrlichia spp. and Rocky Mountain spotted fever titers are indicated for dogs with epistaxis in regions of the country where potential exposure to these rickettsial agents exists. Testing for Bartonella sp. is also considered. Testing for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) should be performed in cats with chronic nasal discharge and potential exposure. Cats infected with FeLV may be predisposed to chronic infection with herpesvirus or calicivirus, whereas those with FIV may have chronic nasal discharge without concurrent infection with these upper respiratory viruses.

Most animals with intranasal disease have normal thoracic radiographs. However, thoracic radiographs may be useful in identifying primary bronchopulmonary disease, pulmonary involvement with cryptococcosis, and rare metastases from neoplastic disease. They may also be a useful preanesthetic screening test for animals that will require nasal imaging, rhinoscopy, and nasal biopsy.

Cytologic evaluation of superficial nasal swabs may identify cryptococcal organisms in cats (see Fig. 13-2). Nonspecific findings include proteinaceous background, moderate



BOX 13-2

General Diagnostic Approach to Dogs and Cats with Chronic Nasal Discharge

Phase I (Noninvasive Testing)				
ALL PATIENTS	DOGS	CATS	DOGS AND CATS WITH HEMORRHAG	
History Physical examination Funduscopic examination Thoracic radiographs	Aspergillus titer	Nasal swab cytologic evalua- tion (cryptococcosis) Cryptococcal antigen titer Viral testing Feline leukemia virus Feline immunodeficiency virus +/- Herpesvirus +/- Calicivirus	Complete blood count Platelet count Coagulation times Buccal mucosal bleeding time Tests for tick-borne diseases (dogs) Arterial blood pressure von Willebrand's factor assay (dogs)	
Phase II—All Patients (Gen	eral Anesthesia Rec	quired)		
Nasal radiography or com Oral examination Rhinoscopy: external nares Nasal biopsy/histologic ex Deep nasal culture Fungal Bacterial	and nasopharynx			
Phase III—All Patients (Ref	erral Usually Requi	red)		
Computed tomography (if	not previously perfo	ormed) or magnetic resonance imag	ing	
Phase IV—All Patients (Cor	sider Referral)			
Repeat Phase II using comp Exploratory rhinotomy with		or magnetic resonance imaging		

to severe inflammation, and bacteria. Tests to identify herpesvirus and calicivirus infections may be performed in cats with acute and chronic rhinitis. These tests are most useful in evaluating cattery problems rather than the condition of an individual cat (see Chapter 15).

Fungal titer determinations are available for aspergillosis in dogs and cryptococcosis in dogs and cats. The test for aspergillosis detects antibodies in the blood. A single positive test result strongly suggests active infection by the organism; however, a negative titer does not rule out the disease. In either case, the result of the test must be interpreted in conjunction with results of nasal imaging, rhinoscopy, and nasal histology and culture.

The blood test of choice for cryptococcosis is the latex agglutination capsular antigen test (LCAT). Because organism identification is usually possible in specimens from infected organs, organism identification is the method of choice for a definitive diagnosis. The LCAT is performed if cryptococcosis is suspected but an extensive search for the organism has failed. The LCAT is also performed in animals with a confirmed diagnosis as a means of monitoring therapeutic response (see Chapter 98).

In general, nasal radiography or computerized tomography (CT), rhinoscopy, and biopsy are required to establish a diagnosis of intranasal disease in most dogs and in cats in

which acute viral infection is not suspected. These diagnostic tests are performed with the dog or cat under general anesthesia. Nasal radiographs or CT scans are obtained first, followed by oral examination and rhinoscopy and then specimen collection. This order is recommended because the results of radiography or CT and rhinoscopy are often useful in the selection of biopsy sites. In addition, hemorrhage from biopsy sites could obscure or alter radiographic and rhinoscopic detail if the specimen were collected first. In dogs and cats suspected of having acute foreign body inhalation, rhinoscopy is performed first in the hopes of identifying and removing the foreign material. (See Chapter 14 for more detail on nasal radiography, CT, and rhinoscopy.)

The combination of radiography, rhinoscopy, and nasal biopsy has a diagnostic success rate of approximately 80% in dogs. Dogs with persistent signs in which a diagnosis cannot be obtained following the assessment described earlier require further evaluation. It is more difficult to evaluate the success rate for cats. High proportions of cats with chronic nasal discharge suffer from feline chronic rhinosinusitis (idiopathic rhinitis) and are diagnosed only through exclusion. Cats are evaluated further only if signs suggestive of another disease are found during any part of their evaluation or if the clinical signs are progressive or intolerable to the owners.

Nasal CT is considered if not performed previously and if a diagnosis has not been made. CT provides excellent visualization of all of the nasal turbinates and may allow the identification of small masses that are not visible on nasal radiography or rhinoscopy. CT is also more accurate than nasal radiography in determining the extent of nasal tumors. Magnetic resonance imaging (MRI) may be more accurate than CT in the assessment of soft tissues, such as nasal neoplasia. In the absence of a diagnosis, nasal imaging (preferably CT or MRI), rhinoscopy, and biopsy can be repeated after a 1- to 2-month delay.

Exploratory rhinotomy with turbinectomy is the final diagnostic test. Surgical exploration of the nose allows direct visualization of the nasal cavity for the presence of foreign bodies, mass lesions, or fungal mats and for obtaining biopsies and culture specimens. The potential benefits of surgery, however, should be weighed against the potential complications associated with rhinotomy and turbinectomy. The Suggested Readings section offers surgical references.

#### **SNEEZING**

# **Etiology and Diagnostic Approach**

A sneeze is an explosive release of air from the lungs through the nasal cavity and mouth. It is a protective reflex to expel irritants from the nasal cavity. Intermittent, occasional sneezing is considered normal. Persistent, paroxysmal sneezing should be considered abnormal. Disorders commonly associated with acute-onset, persistent sneezing include nasal foreign body and feline upper respiratory infection. The canine nasal mite, *Pneumonyssoides caninum*, and exposure to irritating aerosols are less common causes of sneezing. All the nasal diseases considered as differential diagnoses for nasal discharge are also potential causes for sneezing; however, animals with these diseases generally present with nasal discharge as the primary complaint.

The owners should be questioned carefully concerning the possible recent exposure of the pet to foreign bodies (e.g., rooting in the ground, running through grassy fields), powders, and aerosols or, in cats, exposure to new cats or kittens. Sneezing is an acute phenomenon that often subsides with time. A foreign body should not be excluded from the differential diagnoses just because the sneezing subsides. In the dog a history of acute sneezing followed by the development of a nasal discharge is suggestive of a foreign body.

Other findings may help narrow the list of differential diagnoses. Dogs with foreign bodies may paw at their nose. Foreign bodies are typically associated with unilateral, mucopurulent nasal discharge, although serous or serosanguineous discharge may be present initially. Foreign bodies in the caudal nasopharynx may cause gagging, retching, or reverse sneezing. The nasal discharge associated with reactions to aerosols, powders, or other inhaled irritants is usually bilateral and serous in nature. In cats other clinical signs supportive of a diagnosis of upper respiratory infection, such as

conjunctivitis and fever, may be present as well as a history of exposure to other cats or kittens.

Dogs in which acute, paroxysmal sneezing develops should undergo prompt rhinoscopic examination (see Chapter 14). With time, foreign material may become covered with mucus or migrate deeper into the nasal passages, and any delay in performing rhinoscopy may interfere with the identification and removal of the foreign bodies. Nasal mites are also identified rhinoscopically. In contrast, cats sneeze more often as a result of acute viral infection rather than a foreign body. Immediate rhinoscopic examination is not indicated unless there has been known exposure to a foreign body or the history and physical examination findings do not support a diagnosis of viral upper respiratory infection.

#### REVERSE SNEEZING

Reverse sneezing is a paroxysm of noisy, labored inspiration initiated by nasopharyngeal irritation. Such irritation can be the result of a foreign body located dorsal to the soft palate or nasopharyngeal inflammation. Foreign bodies usually originate from grass or plant material that is prehended into the oral cavity and which, presumably, is coughed up or migrates into the nasopharyx. Epiglottic entrapment of the soft palate has also been proposed as a cause. The majority of cases are idiopathic. Small-breed dogs are usually affected, and signs may be associated with excitement or drinking. The paroxysms last only a few seconds and do not significantly interfere with respiration. Although these animals usually display this sign throughout their life, the problem rarely progresses.

The diagnosis is generally made by a thorough history and physical examination. Generally, no treatment is needed because the episodes are self-limiting. Some owners report that massaging the neck shortens an ongoing episode or that administration of antihistamines decreases the frequency and severity of episodes, but controlled studies are lacking. Further evaluation for potential nasal or pharyngeal disorders is indicated if syncope, exercise intolerance, or other signs of respiratory disease are reported or if the reverse sneezing is severe or progressive.

#### **STERTOR**

Stertor refers to coarse, audible snoring or snorting sounds associated with breathing. It indicates upper airway obstruction. Stertor is most often the result of pharyngeal disease (see Chapter 16). Intranasal causes of stertor include obstruction caused by congenital deformities, masses, exudate, or blood clots. Evaluation for nasal disease proceeds as described for nasal discharge.

# **FACIAL DEFORMITY**

Carnaissal tooth root abscess in dogs can result in swelling, often with drainage, adjacent to the nasal cavity and beneath



Facial deformity characterized by firm swelling over the maxilla in two cats. **A**, Deformity in this cat was the result of carcinoma. Notice the ipsilateral blepharospasm. **B**, Deformity in this cat was the result of cryptococcosis. A photomicrograph of the fine-needle aspirate of this swelling is provided in Fig. 13-2.

the eye. Excluding dental disease, the most common causes of facial deformity adjacent to the nasal cavity are neoplasia and, in cats, cryptococcosis (Fig. 13-4). Visible swellings can often be evaluated directly through fine-needle aspiration or punch biopsy (see Fig. 13-2). Further evaluation proceeds as for nasal discharge if such an approach is not possible or is unsuccessful.

## **Suggested Readings**

Demko JL et al: Chronic nasal discharge in cats, J Am Vet Med Assoc 230:1032, 2007.

Fossum TW: Small animal surgery, ed 3, St Louis, 2007, Mosby.

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Lent SE et al: Evaluation of rhinoscopy and rhinoscopy-assisted mucosal biopsy in diagnosis of nasal disease in dogs: 119 cases (1985-1989), *J Am Vet Med Assoc* 201:1425, 1992.

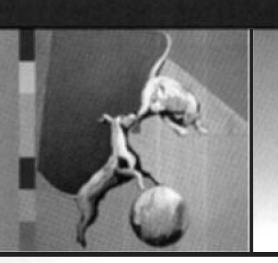
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# CHAPTER

# Diagnostic Tests for the Nasal Cavity and Paranasal Sinuses



# CHAPTER OUTLINE

NASAL IMAGING

Radiography

Computed Tomography and Magnetic Resonance

Imaging

RHINOSCOPY

NASAL BIOPSY: INDICATIONS AND TECHNIQUES

Nasal Swab Nasal Flush Pinch Biopsy Turbinectomy

NASAL CULTURES: SAMPLE COLLECTION AND

INTERPRETATION

## NASAL IMAGING

Nasal imaging is a key component of the diagnostic assessment of animals with signs of intranasal disease, allowing assessment of bone and soft tissue structures that are not visible by physical examination or rhinoscopy. Nasal radiography is the type of imaging most readily available and is described in some detail. However, computed tomography (CT) provides images that are superior to radiographs in the majority of cases. The role of magnetic resonance imaging (MRI) in the evaluation of canine and feline nasal disease has not been well established, but it likely provides more accurate images of soft tissue than does CT. MRI is not used routinely on account of its limited availability and relatively high expense.

Because nasal imaging rarely provides a definitive diagnosis, it is usually followed by rhinoscopy and nasal biopsy. All of these procedures require general anesthesia. Imaging should be performed before, rather than after, these procedures for two reasons: (1) The results of nasal imaging help the clinician direct biopsy instruments to the most abnormal regions, and (2) rhinoscopy and biopsy cause hemorrhage, which obscures soft tissue detail.

#### RADIOGRAPHY

Nasal radiographs are useful for identifying the extent and severity of disease, localizing sites for biopsy within the nasal cavity, and prioritizing the differential diagnoses. The dog or cat must be anesthetized to prevent motion and facilitate positioning. Radiographic abnormalities are often subtle. At least four views should be taken: lateral, ventrodorsal, intraoral, and frontal sinus or skyline. Radiographs of the tympanic bullae are obtained in cats because of the frequent occurrence of otitis media in cats with nasal disease (Detweiler et al., 2006). Determination of involvement of the middle ear is particularly important in cats with suspected nasopharyngeal polyps. Lateral-oblique views or dental films are also indicated in dogs and cats with possible tooth root abscess. The intraoral view is particularly helpful for detecting subtle asymmetry between the left and right nasal cavities.

The intraoral view is taken with the animal in sternal recumbency. The corner of a nonscreen film is placed above the tongue as far into the oral cavity as possible, and the radiographic beam is positioned directly above the nasal cavity (Figs. 14-1 and 14-2). The frontal sinus view is obtained with the animal in dorsal recumbency. Adhesive tape can be used to support the body and draw the forelimbs caudally, out of the field. The head is positioned perpendicular to the spine and the table by drawing the muzzle toward the sternum with adhesive tape. Endotracheal tube and anesthetic tubes are displaced lateral to the head to remove them from the field. A radiographic beam is positioned directly above the nasal cavity and frontal sinuses (Figs. 14-3 and 14-4). The frontal sinus view identifies disease involving the frontal sinuses, which in diseases such as aspergillosis or neoplasia may be the only area of disease involvement. The tympanic bullae are best seen with an open-mouth projection in which the beam is aimed at the base of the skull (Figs. 14-5 and 14-6). The bullae are also evaluated individually by lateral-oblique films, offsetting each bulla from the surrounding skull.

Nasal radiographs are evaluated for increased fluid density, loss of turbinates, lysis of facial bones, radiolucency at the tips of the tooth roots, and the presence of radiodense

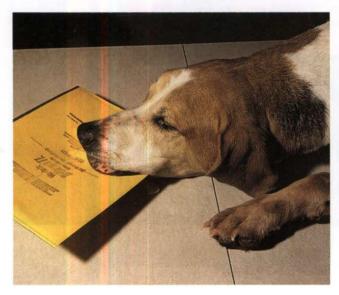


FIG 14-1
Positioning of a dog for intraoral radiographs.

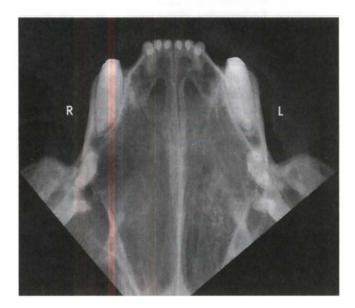


FIG 14-2
Intraoral radiograph of a cat with carcinoma. Normal fine turbinate pattern is visible on the left side (L) of nasal cavity and provides basis for comparison with the right side (R). Turbinate pattern is less apparent on right side, and an area of turbinate lysis can be seen adjacent to the first premolar.

foreign bodies (Box 14-1). Increased fluid density can be caused by mucus, exudate, blood, or soft tissue masses such as polyps, tumors, or granulomas. Soft tissue masses may appear localized, but the surrounding fluid often obscures their borders. A thin rim of lysis surrounding a focal density may represent a foreign body. Fluid density within the frontal sinuses may represent normal mucus accumulation caused by obstruction of drainage into the nasal cavity, extension of disease into the frontal sinuses from the nasal cavity, or primary disease involving the frontal sinuses.

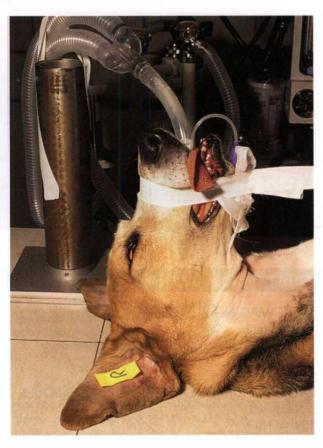


FIG 14-3
Positioning of a dog for frontal sinus radiographs. The endotracheal and anesthetic tubes are displaced laterally in this instance by taping them to an upright metal cylinder.

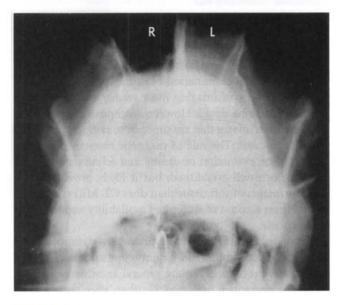
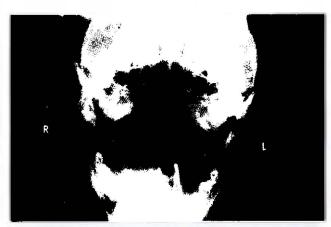


FIG 14-4
Frontal sinus view of a dog with a nasal tumor. The left frontal sinus (L) has increased soft tissue density compared with the air-filled sinus on the right side (R).



Positioning of a cat for open-mouth projection of the tympanic bullae. Beam (arrow) is aimed through the mouth toward the base of the skull. Adhesive tape (t) is holding head and mandible in position.



**FIG 14-6**Radiograph obtained from a cat with nasopharyngeal polypusing the open-mouth projection demonstrated in Fig. 14-5. The left bulla has thickening of bone and increased fluid density, indicating bulla osteitis and probable extension of the polyp.



FIG 14-7
Intraoral radiograph of a dog with nasal aspergillosis. Focal areas of marked turbinate lysis are present on both sides of the nasal cavity. The vomer bone remains intact.

Loss of the normal fine turbinate pattern in combination with increased fluid density within the nasal cavity can occur with chronic inflammatory conditions of any etiology. Early neoplastic changes can also be associated with an increase in soft tissue density and destruction of the turbinates (see Figs. 14-2 and 14-4). More aggressive neoplastic changes may include marked lysis or deformation of the vomer and/or facial bones. Multiple, well-defined lytic zones within the nasal cavity and increased radiolucency in the rostral portion of the nasal cavity suggest aspergillosis (Fig. 14-7). The vomer bone may be roughened but is rarely destroyed. Previous traumatic fracture of the nasal bones and secondary osteomyelitis can also be detected radiographically.

# COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

CT provides excellent visualization of the nasal turbinates, nasal septum, hard palate, and cribriform plate (Fig. 14-8). In cats CT is also useful for determining middle ear involvement with nasopharyngeal polyps or other nasal disease. CT is more accurate than conventional radiography in assessing the extent of neoplastic disease insofar as it allows more



BOX 14-1

Radiographic Signs of Common Nasal Diseases\*

#### Feline Chronic Rhinosinusitis

Soft tissue opacity within nasal cavity, possibly asymmetric Mild turbinate lysis

Soft tissue opacity in frontal sinus(es)

#### Nasopharyngeal Polyp

Soft tissue opacity above soft palate Soft tissue opacity within nasal cavity, usually unilateral Mild turbinate lysis possible

Bulla osteitis: soft tissue opacity within bulla, thickening of

#### Nasal Neoplasia

Soft tissue opacity, possibly asymmetric Turbinate destruction Vomer bone and/or facial bone destruction Soft tissue mass external to facial bones

#### **Nasal Aspergillosis**

Well-defined lucent areas within the nasal cavity Increased radiolucency rostrally Increased soft tissue opacity possibly also present No destruction of vomer or facial bones, although signs often Vomer bone sometimes roughened

Fluid density within the frontal sinus; frontal bones sometimes thickened or moth-eaten

#### Cryptococcosis

Soft tissue opacity, possibly asymmetric Turbinate lysis Facial bone destruction Soft tissue mass external to facial bones

#### Canine Chronic/Lymphoplasmacytic Rhinitis

Soft tissue opacity Lysis of nasal turbinates, especially rostrally

#### **Allergic Rhinitis**

Increased soft tissue opacity Mild turbinate lysis possible

#### Tooth Root Abscesses

Radiolucency adjacent to tooth roots, commonly apically

#### Foreign Bodies

Mineral and metallic dense foreign bodies readily identified Plant foreign bodies: focal, ill-defined, increased soft tissue

Lucent rim around abnormal tissue (rare)

accurate localization of mass lesions for subsequent biopsy than nasal radiography, and it is instrumental for radiotherapy treatment planning. Determination of the integrity of the cribriform plate is important in treatment planning for nasal aspergillosis. CT may also identify the presence of lesions in animals with undiagnosed nasal disease when other techniques have failed. Typical lesions are as described in Box 14-1. MRI may be more accurate than CT in the assessment of soft tissues, such as nasal neoplasia.

#### RHINOSCOPY

Rhinoscopy allows visual assessment of the nasal cavity through the use of a rigid or flexible endoscope or an otoscopic cone. Rhinoscopy is used to visualize and remove foreign bodies; to grossly assess the nasal mucosa for the presence of inflammation, turbinate erosion, mass lesions, fungal plaques, and parasites; and to aid in the collection of nasal specimens for histopathologic examination and culture. Complete rhinoscopy always includes a thorough examination of the oral cavity and caudal nasopharynx, in addition to visualization of the nasal cavity through the external nares.

The extent of visualization depends on the quality of the equipment and the outside diameter of the rhinoscope. A narrow (2- to 3-mm diameter), rigid fiberoptic endoscope provides good visualization through the external nares in most patients. Endoscopes without biopsy or suction channels are preferable because of their small outside diameter. Some of these systems are relatively inexpensive, including one model that can be attached to a standard otoscope handle for the light source (Fig. 14-9). Scopes designed for arthroscopy, cystoscopy, and sexing of birds also work well. In medium to large dogs, a flexible pediatric bronchoscope (e.g., 4-mm outer diameter) can be used. Flexible endoscopes are now available in smaller sizes, similar to small rigid scopes, although they are relatively more expensive and fragile. If an endoscope is not available, the rostral region of the nasal cavity can be examined with an otoscope. Human pediatric otoscopic cones (2- to 3-mm diameter) can be purchased for examining cats and small dogs.

General anesthesia is required for rhinoscopy. Rhinoscopy is usually performed immediately after nasal imaging unless a foreign body is strongly suspected. The oral cavity and caudal nasopharynx should be assessed first. During the oral examination the hard and soft palates are visually examined and palpated for deformation, erosions, or defects, and the gingival sulci are probed for fistulae.

The caudal nasopharynx is evaluated for the presence of nasopharyngeal polyps, neoplasia, and foreign bodies. Foreign bodies, particularly grass or plant material, are commonly found in this location in cats and occasionally in dogs.

<sup>\*</sup> Note that these descriptions represent typical cases and are not specific findings.

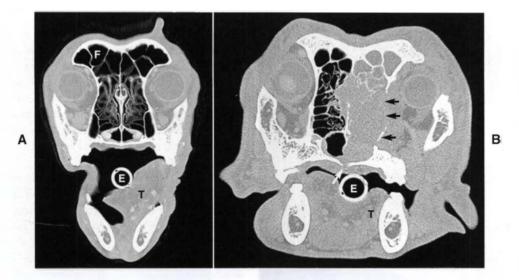
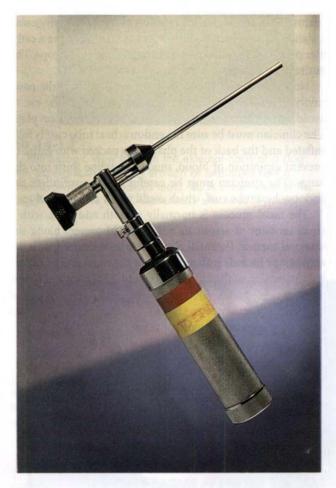


FIG 14-8

CT scans of nasal cavity of two different dogs at the level of the eyes. **A,** Normal nasal turbinates and intact nasal septum are present. **B,** Neoplastic mass is present within the right cavity; it is eroding through the hard palate (white arrow), the frontal bone into the retrobulbar space (small black arrows), and the nasal septum. The tumor also extends into the right frontal sinus. F, Frontal sinus; E, endotracheal tube; T, tongue.



Rigid endoscope (diameter, 3.5 mm; length, 4 inches) suitable for rhinoscopy that uses a standard otoscope handle as a light source. (MDS, Inc., Brandon, Fla.)



FIG 14-10

The caudal nasopharynx is best examined with a flexible endoscope that is passed into the oral cavity and retroflexed 180 degrees around the edge of the soft palate, as shown in this radiograph.

The caudal nasopharynx is best visualized with a flexible endoscope that is passed into the oral cavity and retroflexed around the soft palate (Figs. 14-10 through 14-12). Alternatively, the caudal nasopharynx can be evaluated with the aid of a dental mirror, penlight, and spay hook, which is attached to the caudal edge of the soft palate and pulled forward to improve visualization of the area. It may be possible to visualize nasal mites of infected dogs by observing the caudal nasopharynx while flushing anesthetic gases (e.g., halothane and oxygen) through the nares.

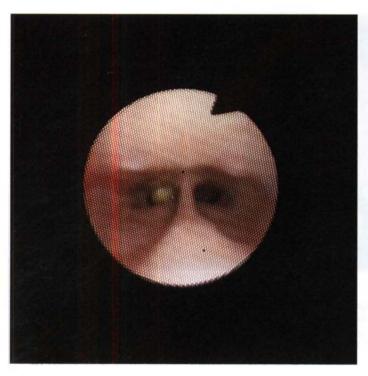
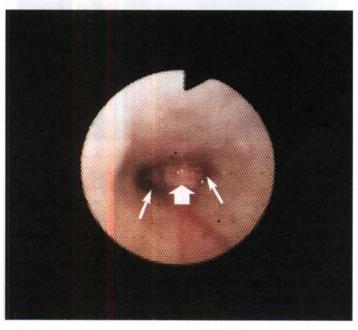


FIG 14-11

View of the internal nares obtained by passing a flexible bronchoscope around the edge of the soft palate in a dog with sneezing. A small white object is seen within the left nasal cavity adjacent to the septum. Note that the septum is narrow and the right internal naris is oval in shape and not obstructed. On removal, the object was found to be a popcorn kernel. The dog had an abnormally short soft palate, and the kernel presumably entered the caudal nasal cavity from the oropharynx.



HG 14-12

View of the internal nares (thin arrows) obtained by passing a flexible bronchoscope around the edge of the soft palate in a dog with nasal discharge. A soft tissue mass (broad arrow) is blocking the normally thin septum and is partially obstructing the airway lumens. Compare this view with the appearance of the normal septum and right internal naris in Fig. 14-11

Rhinoscopy must be performed patiently, gently, and thoroughly to maximize the likelihood of identifying gross abnormalities and minimize the risk of hemorrhage. The more normal side of the nasal cavity is examined first. The tip of the scope is passed through the naris with the tip pointed medially. Each nasal meatus is evaluated, beginning ventrally and working dorsally to ensure visualization should hemorrhage develop during the procedure. Each nasal meatus should be examined as far caudally as the scope can be passed without trauma.

Although the rhinoscope can be used to evaluate the large chambers of the nose, many of the small recesses cannot be examined, even with the smallest endoscopes. Thus disease or a foreign body may be missed if only these small recesses are involved. Swollen and inflamed nasal mucosa, hemorrhage caused by the procedure, and the accumulation of exudate and mucus can also interfere with visualization of the nasal cavity. Foreign bodies and masses are frequently coated and effectively hidden by seemingly insignificant amounts of mucus, exudate, or blood. The tenacious material must be removed using a rubber catheter with the tip cut off attached to a suction unit. If necessary, saline flushes can also be used, although resulting fluid bubbles may further interfere with visualization. Some clinicians prefer to maintain continuous saline infusion of the nasal cavity using a standard intravenous administration set attached to a catheter or, if available, the biopsy channel of the rhinoscope. The entire examination is done "under water."

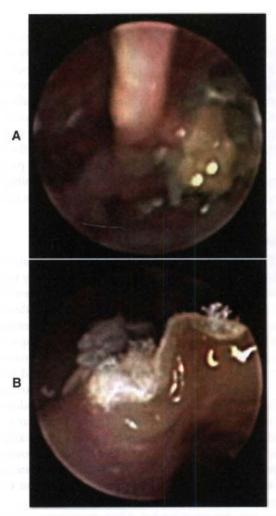
No catheter should ever be passed blindly into the nasal cavity beyond the level of the medial canthus of the eye to avoid entering the cranial vault through the cribriform plate. The clinician must be sure the endotracheal tube cuff is fully inflated and the back of the pharynx is packed with gauze to prevent aspiration of blood, mucus, or saline flush into the lungs. The clinician must be careful not to overinflate the endotracheal tube cuff, which could result in a tracheal tear.

The nasal mucosa is normally smooth and pink, with a small amount of serous to mucoid fluid present along the mucosal surface. Potential abnormalities visualized with the rhinoscope include inflammation of the nasal mucosa; mass lesions; erosion of the turbinates (Fig. 14-13, *A*); mats of fungal hyphae (Fig. 14-13, *B*); foreign bodies; and, rarely, nasal mites or *Capillaria* worms (Fig. 14-14). Differential diagnoses for gross rhinoscopic abnormalities are provided in Box 14-2.

The location of any abnormality should be noted, including the meatus involved (common, ventral, middle, dorsal), the medial-to-lateral orientation within the meatus, and the distance caudal from the naris. Exact localization is critical for directing instruments for the retrieval of foreign bodies or nasal biopsy should visual guidance become impeded by hemorrhage or size of the cavity.

# NASAL BIOPSY: INDICATIONS AND TECHNIQUES

Visualization of a foreign body or nasal parasites during rhinoscopy establishes a diagnosis. For many dogs and cats,



**FIG 14-13 A,** Rhinoscopic view through the external naris of a dog with aspergillosis showing erosion of turbinates and a green-brown granulomatous mass. **B,** A closer view of the fungal mat shows white, filamentous structures (hyphae).



# BOX 14-2

Differential Diagnoses for Gross Rhinoscopic Abnormalities in Dogs and Cats

# Inflammation (Mucosal Swelling, Hyperemia, Increased Mucus, Exudate)

Nonspecific finding; consider all differential diagnoses for mucopurulent nasal discharge (infectious, inflammatory, neoplastic)

#### Mass

Neoplasia

Nasopharyngeal polyp

Cryptococcosis

Mat of fungal hyphae or fungal granuloma (aspergillosis, penicilliosis, rhinosporidiosis)

#### **Turbinate Erosion**

Mild

Feline herpesvirus

Chronic inflammatory process

Marked

Aspergillosis

Neoplasia

Cryptococcosis

Penicilliosis

#### **Fungal Plaques**

Aspergillosis

Penicilliosis

#### **Parasites**

Mites: Pneumonyssoides caninum

Worms: Capillaria (Eucoleus) boehmi

#### **Foreign Bodies**





-

FIG 14-14

Rhinoscopic view through the external naris. **A,** A single nasal mite is seen in this dog with *Pneumonyssoides caninum*. **B,** A thin white worm is seen in this dog with *Capillaria* (Eucoleus) boehmi.

however, the diagnosis must be based on cytologic, histologic, and microbiologic evaluation of nasal biopsy specimens. Nasal biopsy specimens should be obtained immediately after nasal imaging and rhinoscopy while the animal is still anesthetized. These earlier procedures can help localize the lesion, maximizing the likelihood of obtaining material representative of the primary disease process.

Nasal biopsy techniques include nasal swab, nasal flush, pinch biopsy, and turbinectomy. Fine-needle aspirates can be obtained from mass lesions as described in Chapter 75. Pinch biopsy is the preferred nonsurgical method of specimen collection. It is more likely to provide pieces of nasal tissue that extend beneath the superficial inflammation, which is common to many nasal disorders, than nasal swabs or flushes. In addition, the pieces of tissue obtained with this more aggressive method can be evaluated histologically, whereas the material obtained with the less traumatic techniques may be suitable only for cytologic analysis. Histopathologic examination is preferred over cytologic examination in most cases because the marked inflammation that accompanies many nasal diseases makes it difficult to cytologically differentiate primary from secondary inflammation and reactive from neoplastic epithelial cells. Carcinomas can also appear cytologically as lymphoma and vice versa.

Regardless of the technique used (except for nasal swab), the cuff of the endotracheal tube should be inflated (avoiding overinflation) and the caudal pharynx packed with gauze sponges to prevent the aspiration of fluid. Intravenous crystalloid fluids (10 to 20 ml/kg/h plus replacement of estimated blood loss) are recommended during the procedure to counter the hypotensive effects of prolonged anesthesia and blood loss from hemorrhage after biopsy. Blood-clotting capabilities should be assessed before the more aggressive biopsy techniques are performed if there is any history of hemorrhagic exudate or epistaxis or any other indication of coagulopathy.

# **NASAL SWAB**

The least traumatic techniques are the nasal swab and nasal flush. Unlike the other collection techniques, nasal swabs can be collected from an awake animal. Nasal swabs are useful for identifying cryptococcal organisms cytologically and should be collected early in the evaluation of cats with chronic rhinitis. Other findings are generally nonspecific. Exudate immediately within the external nares or draining from the nares is collected using a cotton-tipped swab. Relatively small swabs are available (e.g., Dacron swabs; Puritan Medical Products Co. LLC) that can facilitate specimen collection from cats with minimal discharge. The swab is then rolled on a microscope slide. Routine cytologic stains are generally used, although India ink can be applied to demonstrate cryptococcal organisms (see Chapter 98).

#### **NASAL FLUSH**

Nasal flush is a minimally invasive technique. A soft catheter is positioned in the caudal region of the nasal cavity via the oral cavity and internal nares, with the tip of the catheter pointing rostrally. With the animal in sternal recumbency and the nose pointed toward the floor, approximately 100 ml of sterile saline solution is forcibly injected in pulses by syringe. The fluid exiting the external nares is collected in a bowl and can be examined cytologically. Occasionally nasal mites can be identified in nasal flushings. Magnification or placement of dark paper behind the specimen for contrast may be needed to visualize the mites. A portion of fluid can also be filtered through a gauze sponge. Large particles trapped in the sponge can be retrieved and submitted for histopathologic analysis. These specimens are often insufficient for providing a definitive diagnosis.

#### PINCH BIOPSY

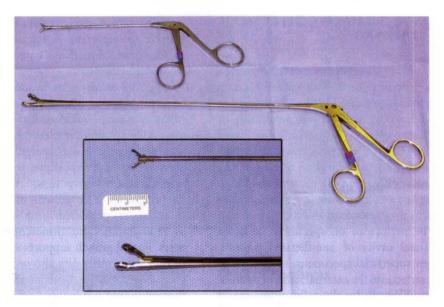
Pinch biopsy is the author's preferred method of nasal biopsy. In the pinch biopsy technique, alligator cup biopsy forceps (minimum size,  $2 \times 3$  mm) are used to obtain pieces of nasal mucosa for histologic evaluation (Fig. 14-15). Full-thickness tissue specimens can be obtained, and guided specimen collection is more easily performed with this technique than with previously described methods. The biopsy forceps are passed adjacent to a rigid endoscope and directed to any gross lesions. If a flexible scope is used, biopsy instruments can be passed through the biopsy channel of the endoscope. The resulting specimens are extremely small and may not be of sufficient quality for diagnostic purposes. Larger alligator forceps are preferred. If lesions are not present grossly but are present radiographically or by CT, the biopsy instrument can be guided using the relationship of the lesion to the upper teeth.

After the first piece is taken, bleeding will prevent further visual guidance; therefore the forceps are passed blindly to the position identified during rhinoscopic examination (e.g., meatus involved and depth from external naris). If a mass is present, the forceps are passed in a closed position until just before the mass is reached. The forceps are then opened and passed a short distance farther until resistance is felt. Larger forceps, such as a mare uterine biopsy instrument, are useful for collecting large volumes of tissue from medium to large size dogs with nasal masses. No forceps should ever be passed into the nasal cavity deeper than the level of the medial canthus of the eye without visual guidance to keep from penetrating the cribriform plate.

A minimum of six tissue specimens (using a  $2 \times 3$  mm forcep or larger) should be obtained from any lesion. If no localizable lesion is identified radiographically or rhinoscopically, multiple biopsies (usually 6 to 10) are obtained randomly from both sides of the nasal cavity.

### **TURBINECTOMY**

Turbinectomy provides the best tissue specimens for histologic examination and allows the clinician to remove abnormal or poorly vascularized tissues, debulk fungal granulomas, and place drains for subsequent topical nasal therapy. Turbinectomy is performed through a rhinotomy incision and is a more invasive technique than those previ-



**FIG 14-15** Cup biopsy forceps are available in different sizes. To obtain sufficient tissue, a minimum size of  $2 \times 3$  mm is recommended. The larger forceps are particularly useful for obtaining biopsies from nasal masses in dogs.

ously described. Turbinectomy is a reasonably difficult surgical procedure that should be considered only when other less invasive techniques have failed to establish the diagnosis. Potential operative and postoperative complications include pain, excessive hemorrhage, inadvertent entry into the cranial vault, and recurrent nasal infections. Cats may be anorectic postoperatively. Placement of an esophagostomy or gastrostomy tube (see Chapter 30) should be considered if necessary to provide a means for meeting nutritional requirements during the recovery period. (See Suggested Readings in Chapter 13 for information on the surgical procedure.)

#### Complications

The major complication associated with nasal biopsy is hemorrhage. The severity of hemorrhage depends on the method used to obtain the biopsy, but even with aggressive techniques the hemorrhage is rarely life threatening. When any technique is used, the floor of the nasal cavity is avoided to prevent damage to major blood vessels. For minor hemorrhage, the rate of administration of intravenous fluids should be increased and manipulations within the nasal cavity should be stopped until the bleeding subsides. Cold saline solution with or without diluted epinephrine (1:100,000) can be gently infused into the nasal cavity. Persistent severe hemorrhage can be controlled by packing the nasal cavity with umbilical tape. The tape must be packed through the nasopharynx as well as through the external nares or the blood will only be redirected. Similarly, placing swabs or gauze in the external nares serves only to redirect blood caudally. In the rare event of uncontrolled hemorrhage, the carotid artery on the involved side can be ligated without subsequent adverse effects. Rhinotomy should not be attempted. In the vast majority of animals, only time or cold saline infusions are required to control hemorrhage. The fear of severe hemorrhage should not prevent the collection of good-quality tissue specimens.

Trauma to the brain is prevented by never passing any object into the nasal cavity beyond the level of the medial canthus of the eye without visual guidance. The distance from the external nares to the medial canthus is noted by holding the instrument or catheter against the face, with the tip at the medial canthus. The level of the nares is marked on the instrument or catheter with a piece of tape or marking pen. The object should never be inserted beyond that mark.

Aspiration of blood, saline solution, or exudate into the lungs must be avoided. A cuffed endotracheal tube should be in place during the procedure, and the caudal pharynx should be packed with gauze after visual assessment of the oral cavity and nasopharynx. The cuff should be sufficiently inflated to prevent audible leakage of air during gentle compression of the reservoir bag of the anesthesia machine. Overinflation of the cuff may lead to tracheal trauma or tear. The nose is pointed toward the floor over the end of the examination table, allowing blood and fluid to drip out from the external nares after rhinoscopy and biopsy. Finally, the caudal pharynx is examined during gauze removal and before extubation for visualization of continued accumulation of fluid. Gauze sponges are counted during placement and then recounted during removal so that none is inadvertently left behind.

# NASAL CULTURES: SAMPLE COLLECTION AND INTERPRETATION

Microbiologic cultures of nasal specimens are recommended but can be difficult to interpret. Aerobic and anaerobic bacterial cultures, mycoplasmal cultures, and fungal cultures can be performed on material obtained by swab, nasal flush, or tissue biopsy. According to Harvey (1984), the normal nasal flora can include *Escherichia coli*, *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Pasteurella*, and *Aspergillus* organisms and a variety of other aerobic and anaerobic bacteria and fungi. Thus bacterial or fungal growth from nasal specimens does not necessarily confirm the presence of infection.

Cultures should be performed on specimens collected within the caudal nasal cavity of anesthetized patients. Bacterial growth from superficial specimens, such as nasal discharge or swabs inserted into the external nares of unanesthetized patients, is unlikely to be clinically significant. It is difficult for a culture swab to be passed into the caudal nasal cavity without its being contaminated with superficial (insignificant) organisms. Guarded specimen swabs can prevent contamination but are relatively expensive. Alternatively, mucosal biopsies from the caudal nasal cavity can be obtained for culture using sterilized biopsy forceps; the results may be more indicative of true infection than those from swabs because, in theory, the organisms have invaded the tissues. Superficial contamination may still occur.

Regardless of the method used, the growth of many colonies of one or two types of bacteria more likely reflects infection than the growth of many different organisms. The microbiology laboratory should be asked to report all growth. Otherwise, the laboratory may report only one or two organisms that are more often pathogenic and provide misleading information about the relative purity of the culture. The presence of septic inflammation based on histologic examination of nasal specimens and a positive response to antibiotic therapy support a diagnosis of bacterial infection contributing to clinical signs. Although bacterial rhinitis is rarely a primary disease entity, improvement in nasal discharge may be seen if the bacterial component of the problem is treated; however, the improvement is generally transient unless the underlying disease process can be corrected. Some animals in which a primary disease process is never identified or cannot be corrected (e.g., cats with chronic rhinosinusitis) respond well to long-term antibiotic therapy. Sensitivity data from bacterial cultures considered to represent significant infection may help in antibiotic selection. (See Chapter 15 for further therapeutic recommendations.)

The role of *Mycoplasma* spp. in respiratory tract infections of dogs and cats is still being elucidated. Cultures for *Mycoplasma* spp. and treatment with appropriate antibiotics are a consideration for cats with chronic rhinosinusitis.

A diagnosis of nasal aspergillosis or penicilliosis requires the presence of several supportive signs, and fungal cultures are indicated whenever fungal disease is one of the differential diagnoses. The growth of Aspergillus or Penicillium organisms is considered along with other clinical data, such as radiographic and rhinoscopic findings, and serologic titers. Fungal growth supports a diagnosis of mycotic rhinitis only when other data also support the diagnosis. The fact that fungal infection occasionally occurs secondary to nasal tumors should not be overlooked during initial evaluation and monitoring of therapeutic response. The sensitivity of fungal culture can be greatly enhanced by collecting a swab or biopsy for culture directly from a fungal plaque or granuloma with rhinoscopic guidance.

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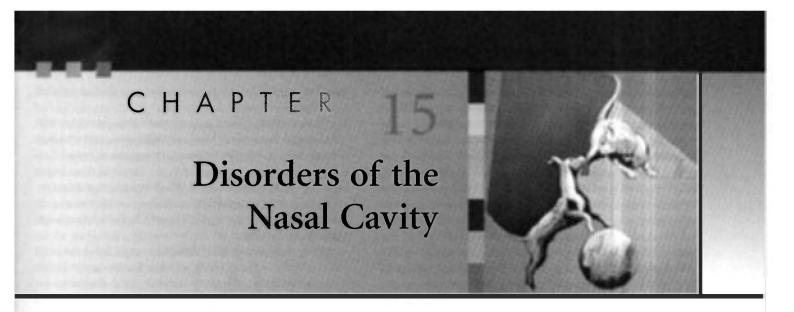
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# CHAPTER OUTLINE

FELINE UPPER RESPIRATORY INFECTION
BACTERIAL RHINITIS
NASAL MYCOSES

Cryptococcosis Aspergillosis NASAL PARASITES

Nasal mites
Nasal capillariasis
NASOPHARYNGEAL POLYPS
NASAL TUMORS
ALLERGIC RHINITIS
IDIOPATHIC RHINITIS
Feline Chronic Rhinosinusitis

Feline Chronic Rhinosinusitis
Canine Chronic/Lymphoplasmacytic Rhinitis

#### FELINE UPPER RESPIRATORY INFECTION

#### Etiology

Upper respiratory infections (URIs) are common in cats. Feline herpesvirus (FHV), also known as *feline rhinotracheitis virus*, and *feline calicivirus* (FCV), cause nearly 90% of these infections. *Bordetella bronchiseptica* and *Chlamydophila felis* (previously known as *Chlamydia psittaci*) are less commonly involved. Other viruses and *Mycoplasmas* may play a primary or secondary role, whereas other bacteria are considered secondary pathogens.

Cats become infected through contact with actively infected cats, carrier cats, and fomites. Cats that are young, stressed, or immunosuppressed are most likely to develop clinical signs. Infected cats often become carriers of FHV or FCV after resolution of the clinical signs. The duration of the carrier state is not known but may last from weeks to years. *Bordetella* can be isolated from asymptomatic cats, although the effectiveness of transmission of disease from such cats is not known.

#### **Clinical Features**

Clinical manifestations of feline URI can be acute, chronic and intermittent, or chronic and persistent. Acute disease is the most common. The clinical signs of acute URI include fever, sneezing, serous or mucopurulent nasal discharge, conjunctivitis and ocular discharge, hypersalivation, anorexia, and dehydration. FHV can also cause corneal ulceration, abortion, and neonatal death, whereas FCV can cause oral ulcerations, mild interstitial pneumonia, or polyarthritis. Rare, short-lived outbreaks of highly virulent strains of calicivirus have been associated with severe upper respiratory disease, signs of systemic vasculitis (facial and limb edema progressing to focal necrosis) and high rates of mortality. Bordetella can cause cough and, in young kittens, pneumonia. Signs of Chlamydophila infection are usually limited to conjunctivitis.

Some cats that recover from the acute disease have periodic recurrence of acute signs, usually in association with stressful or immunosuppressive events. Other cats may have chronic, persistent signs, most notably a serous to mucopurulent nasal discharge with or without sneezing. Chronic nasal discharge can presumably result from persistence of an active viral infection or from irreversible damage to turbinates and mucosa by FHV; the latter predisposes the cat to an exaggerated response to irritants and secondary bacterial rhinitis. Unfortunately, correlation between tests to confirm exposure to or the presence of viruses and clinical signs is poor (Johnson et al., 2005). Because the role of viral infection in cats with chronic rhinosinusitis is not well understood, cats with chronic signs of nasal disease are discussed in the section on feline chronic rhinosinusitis (p. 232).

#### Diagnosis

Acute URI is usually diagnosed on the basis of history and physical examination findings. Specific tests that are available to identify FHV, FCV, *Bordetella*, and *Chlamydophila* organisms include fluorescent antibody testing, virus isolation procedures or bacterial cultures, polymerase chain reaction (PCR), and serum antibody titers. Fluorescent antibody tests for FHV and FCV are performed on smears prepared from conjunctival scrapings, pharyngeal swabs, or tonsillar

swabs or on impression smears from tonsillar biopsy specimens. Virus isolation tests and PCR can be performed on pharyngeal, conjunctival, or nasal swabs (using sterile swabs made of cotton) or on tissue specimens such as tonsillar biopsy specimens or mucosal scraping. Tissue specimens are preferred for virus isolation and PCR. Specimens are placed in appropriate transport media. Routine cytologic preparations of conjunctival smears can be examined for intracytoplasmic inclusion bodies suggestive of Chlamydophila infections, but these findings are nonspecific. Although routine bacterial cultures of the oropharynx can be used to identify Bordetella, the organism can be found in healthy and infected cats. Demonstration of rising antibody titers against a specific agent over 2 to 3 weeks suggests active infection. Regardless of the method used, close coordination with the pathology laboratory on specimen collection and handling is recommended for optimal results.

Tests to identify specific agents are particularly useful in cattery outbreaks in which the clinician is asked to recommend specific preventive measures. Multiple cats, both with and without clinical signs, should be tested when performing cattery surveys. Specific diagnostic tests are less useful for testing individual cats because their results do not alter therapy; false-negative results may occur if signs are the result of permanent nasal damage or if the specimen does not contain the agent, and, positive results may merely reflect a carrier cat that has a concurrent disease process causing the clinical signs. The exception to this generalization is individual cats with suspected *Chlamydophila* infection, in which case specific effective therapy can be recommended.

#### **Treatment**

In most cats URI is a self-limiting disease, and treatment of cats with acute signs includes appropriate supportive care. Hydration and nutritional needs should be provided when necessary. Dried mucus and exudate should be cleaned from the face and nares. The cat can be placed in a steamy bathroom or a small room with a vaporizer for 15 to 20 minutes two or three times daily to help clear excess secretions. Severe nasal congestion is treated with pediatric topical decongestants such as 0.25% phenylephrine or 0.025% oxymetazoline. A drop is gently placed in each nostril daily for a maximum of 3 days. If longer therapy is necessary, the decongestant is withheld for 3 days before beginning another 3-day course to prevent possible rebound congestion after withdrawal of the drug (based on problems with rebound congestion that occurs in people). Another option for prolonged decongestant therapy is to alternate daily the naris treated.

Antibiotic therapy to treat secondary infection is indicated in cats with severe clinical signs. The initial antibiotic of choice is ampicillin (22 mg/kg q8h) or amoxicillin (22 mg/kg q8h to q12h), because they are often effective, are associated with few adverse reactions, and can be administered to kittens. If *Bordetella*, *Chlamydophila*, or *Mycoplasma* spp. is suspected, doxycycline (5 to 10 mg/kg q12h, followed by a bolus of water) or chloramphenicol (10 to 15 mg/kg q12h) should be used. Azithromycin (5 to 10 mg/kg q24h for 3

days, then q72h) can be prescribed for cats that are difficult to medicate.

Cats with FHV infection may benefit from treatment with lysine. It has been postulated that excessive concentrations of lysine may antagonize arginine, a promoter of herpesvirus replication. Lysine (500 mg/cat q12h), obtained from health food stores, is added to food. Administration of feline recombinant omega interferon or human recombinant  $\alpha$ -2b interferon may also be of some benefit in FHV-infected cats (Siebeck et al., 2006).

Chlamydophila infection should be suspected in cats with conjunctivitis as the primary problem and in cats from catteries in which the disease is endemic. Oral antibiotics are administered for 3 weeks. In addition, chloramphenicol or tetracycline ophthalmic ointment should be applied at least three times daily and continued for a minimum of 14 days after the resolution of signs.

Corneal ulcers resulting from FHV are treated with topical antiviral drugs, such as trifluridine, idoxuridine, or adenine arabinoside. One drop should be applied to each affected eye five to six times daily for no longer than 2 to 3 weeks. Routine ulcer management is also indicated. Tetracycline or chloramphenicol ophthalmic ointment is administered two to four times daily. Topical atropine is used for mydriasis as needed to control pain. Treatment is continued for 1 to 2 weeks after epithelialization has occurred.

Topical and systemic corticosteroids are contraindicated in cats with acute URI or ocular manifestations of FHV infection. They can prolong clinical signs and increase viral shedding.

Treatment of cats with chronic signs is discussed on p. 233.

# Prevention in the Individual Pet Cat

Prevention of URI in all cats is based on avoiding exposure to the infectious agents (e.g., FHV, FCV, Bordetella and Chlamydophila organisms) and strengthening immunity against infection. Most household cats are relatively resistant to prolonged problems associated with URIs, and routine health care with regular vaccination using a subcutaneous product is adequate. Vaccination decreases severity of clinical signs resulting from URIs but does not prevent infection. Owners should be discouraged from allowing their cats to roam freely outdoors.

Subcutaneous modified-live virus vaccines for FHV and FCV are used for most cats and are available in combination with panleukopenia vaccine. These vaccines are convenient to administer, do not result in clinical signs when used correctly, and provide adequate protection for cats that are not heavily exposed to these viruses. These vaccines are not effective in kittens while maternal immunity persists. Kittens are usually vaccinated beginning at 6 to 10 weeks of age and again in 3 to 4 weeks. At least two vaccines must be given initially, with the final vaccine administered after the kitten is 16 weeks old. A booster vaccination is recommended 1 year after the final vaccine in the initial series. Subsequent booster vaccinations are recommended every 3 years, unless

the cat has increased risk of exposure to infection. A study by Lappin et al. (2002) indicates that detection of FHV and FCV antibodies in the serum of cats is predictive of susceptibility to disease and therefore may be useful in determining need for revaccination. Queens should be vaccinated before breeding.

Subcutaneous modified-live vaccines for FHV and FCV are safe but can cause disease if introduced into the cat by the normal oronasal route of infection. The vaccine should not be aerosolized in front of the cat. Vaccine inadvertently left on the skin after injection should be washed off immediately before the cat licks the area.

Modified-live vaccines should not be used in pregnant queens. Killed products are available for FHV and FCV that can be used in pregnant queens. Killed vaccines have also been recommended for cats with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection.

Modified-live vaccines for FHV and FCV are also available for intranasal administration. Signs of acute URI occasionally occur after vaccination. Attention should be paid to ensure that panleukopenia is included in the intranasal product or that a panleukopenia vaccine is administered subcutaneously.

Vaccines against *Bordetella* or *Chlamydophila* are recommended for use only in catteries or shelters where these infections are endemic. Infections with *Bordetella* or *Chlamydophila* are less common than FHV and FCV infection, and disease resulting from *Bordetella* infections occurs primarily in cats housed in crowded conditions. Furthermore, these diseases can be effectively treated with antibiotics.

#### **Prognosis**

The prognosis for cats with acute URI is good. Chronic disease does not develop in most pet cats.

#### **BACTERIAL RHINITIS**

Acute bacterial rhinitis caused by *Bordetella bronchiseptica* occurs occasionally in cats (see the section on feline upper respiratory infection) and rarely in dogs (see the section on canine infectious tracheobronchitis in Chapter 21). It is possible that *Mycoplasma* can act as primary nasal pathogens. In the vast majority of cases, bacterial rhinitis is a *secondary* complication and not a primary disease process. Bacterial rhinitis occurs secondarily to almost all diseases of the nasal cavity. The bacteria that inhabit the nasal cavity in health are quick to overgrow when disease disrupts normal mucosal defenses. Antibiotic therapy often leads to clinical improvement, but the response is usually temporary. Therefore management of dogs and cats with suspected bacterial rhinitis should include a thorough diagnostic evaluation for an underlying disease process, particularly when signs are chronic.

#### **Diagnosis**

Most dogs and cats with bacterial rhinitis have mucopurulent nasal discharge. No clinical signs are pathognomonic for

bacterial rhinitis, and it is difficult to make a definitive diagnosis because of the diverse flora in the normal nasal cavity (see Chapter 14). Microscopic evidence of neutrophilic inflammation and bacteria is a nonspecific finding in the majority of animals with nasal signs (Fig. 15-1). Bacterial cultures of swabs or nasal mucosal biopsies collected deep within the nasal cavity can be performed. The growth of many colonies of only one or two organisms may represent significant infection. Growth of many different organisms or small numbers of colonies probably represents normal flora. The microbiology laboratory should be requested to report all growth. Specimens for Mycoplasmal cultures should be placed in appropriate transport media for culture using specific isolation methods. Beneficial response to antibiotic therapy is often used to support a diagnosis of bacterial involvement.

#### **Treatment**

The bacterial component of nasal disease is treated with antibiotic therapy. If growth obtained by bacterial culture is believed to be significant, sensitivity information can be used in selecting antibiotics. Anaerobic organisms may be involved. Broad-spectrum antibiotics that may be effective include amoxicillin (22 mg/kg q8-12h), trimethoprim-sulfadiazine (15 mg/kg q12h), chloramphenicol (50 mg/kg q8h for dogs; 10 to 15 mg/kg q12h for cats), or clindamycin (5.5 to 11 mg/kg q12h). Doxycycline (5 to 10 mg/kg q12h, followed by a bolus of water) or chloramphenicol is often effective against *Bordetella* and *Mycoplasma* organisms.

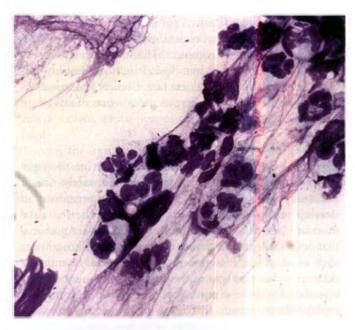


FIG 15-1

A photomicrograph of a slide prepared from a nasal swab of a patient with chronic mucopurulent discharge shows the typical findings of mucus, neutrophilic inflammation, and intracellular and extracellular bacteria. These findings are not specific and generally reflect secondary processes.

For acute infection or in cases in which the primary etiology (e.g., foreign body, diseased tooth root) has been eliminated, antibiotics are administered for 7 to 10 days. Chronic infections require prolonged treatment. Antibiotics are administered initially for 1 week. If a beneficial response is seen, the drug is continued for a minimum of 4 to 6 weeks. If signs recur after discontinuation of drug after 4 to 6 weeks, the same antibiotic is reinstituted for even longer periods.

If no response is seen after the initial week of treatment, the drug should be discontinued. Another antibiotic can be tried, although further evaluation for another, as yet unidentified, primary disorder should be pursued. Further diagnostic evaluation is particularly warranted in dogs because, compared with cats, they less frequently have idiopathic disease. Frequent stopping and starting of different antibiotics every 7 to 14 days is not recommended and may predispose the animal to the growth of resistant gram-negative infections.

#### **Prognosis**

Bacterial rhinitis is usually responsive to antibiotic therapy. However, long-term resolution of signs depends on the identification and correction of any underlying disease process.

#### NASAL MYCOSES

#### **CRYPTOCOCCOSIS**

Cryptococcus neoformans is a fungal agent that infects cats and, less commonly, dogs. It most likely enters the body through the respiratory tract and, in some animals, may disseminate to other organs. In cats clinical signs usually reflect infection of the nasal cavity, central nervous system (CNS), eyes, or skin and subcutaneous tissues. In dogs signs of CNS involvement are most common. The lungs are commonly infected in both species, but clinical signs of lung involvement (e.g., cough, dyspnea) are rare. Clinical features, diagnosis, and treatment of cryptococcosis are discussed in Chapter 98.

#### **ASPERGILLOSIS**

Aspergillus fumigatus is a normal inhabitant of the nasal cavity in many animals. In some dogs and, rarely, cats, it becomes a pathogen. The mold form of the organism can develop into visible fungal plaques that invade the nasal mucosa ("fungal mats") and fungal granulomas. An animal that develops aspergillosis may have another nasal condition, such as neoplasia, foreign body, prior trauma, or immune deficiency that predisposes the animal to secondary fungal infection. Excessive exposure to Aspergillus organisms may explain the frequent occurrence of disease in otherwise healthy animals. Another type of fungus, Penicillium, can cause signs similar to those of aspergillosis.

#### **Clinical Features**

Aspergillosis can cause chronic nasal disease in dogs of any age or breed but is most common in young male dogs. Nasal

infection is rare in cats. The discharge can be mucoid, mucopurulent with or without hemorrhage, or purely hemorrhagic. The discharge can be unilateral or bilateral. Sneezing may be reported. Features that are highly suggestive of aspergillosis are sensitivity to palpation of the face or depigmentation and ulceration of the external nares (see Fig. 13-1). Lung involvement is not expected.

Systemic aspergillosis in dogs is generally caused by *Aspergillus terreus* and other *Aspergillus* spp. rather than *A. fumigatus*. It is an unusual, generally fatal disease that occurs primarily in German Shepherd Dogs. Nasal signs are not reported.

#### Diagnosis

No single test result is diagnostic for infection with aspergillosis. The diagnosis is based on the cumulative findings of a comprehensive evaluation of a dog with appropriate clinical signs. In addition, aspergillosis can be an opportunistic infection, and underlying nasal disease must always be considered.

Radiographic signs of aspergillosis include well-defined lucent areas within the nasal cavity and increased radiolucency rostrally (see Fig. 14-7). Typically no destruction of the vomer or facial bones occurs, although the bones may appear roughened. However, destruction of these bones or the cribriform plate may occur in dogs with advanced disease. Increased fluid opacity may be present. Fluid opacity within the frontal sinus can represent a site of infection or mucus accumulation from obstructed drainage. In some patients the frontal sinus is the only site of infection.

Rhinoscopic abnormalities include erosion of nasal turbinates and fungal plaques, which appear as white-to-green plaques of mold on the nasal mucosa (see Fig. 14-13). Failure to visualize these lesions does not rule out aspergillosis. Confirmation that presumed plaques are indeed fungal hyphae can be achieved by cytology (Fig. 15-2) and culture of material collected by biopsy or swab under visual guidance. During rhinoscopy, plaques are mechanically debulked by

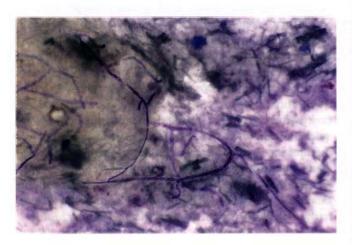


FIG 15-2
Branching hyphae of Aspergillus fumigatus from a swab of a visualized fungal plaque.

scraping or vigorous flushing to increase the efficacy of topical treatment.

Aspergillus organisms can generally be seen histologically in biopsy specimens of affected nasal mucosa after routine staining techniques, although special staining can be performed to identify subtle involvement. Neutrophilic, lymphoplasmacytic, or mixed inflammation is usually also present. Multiple biopsy specimens should be obtained because the mucosa is affected multifocally rather than diffusely. Invasion of fungal organisms into the nasal mucosa is indicative of infection.

Results of fungal cultures are difficult to interpret, unless the specimen is obtained from a visualized plaque. The organism can be found in the nasal cavity of normal animals, and false-negative culture results can also occur. A positive culture, in conjunction with other appropriate clinical and diagnostic findings, supports the diagnosis.

Positive serum antibody titers also support a diagnosis of infection. Although titers are indirect evidence of infection, animals with *Aspergillus* organisms as a normal nasal inhabitant do not usually develop measurable antibodies against the organism. Pomerantz et al. (2007) found that serum antibodies had a sensitivity of 67%, a specificity of 98%, a positive predictive value of 98%, and a negative predictive value of 84% for the diagnosis of nasal aspergillosis. Their study included 21 dogs with aspergillosis, 25 dogs with nonfungal rhinitis, and 12 dogs with nasal neoplasia.

#### **Treatment**

The current treatments of choice for nasal aspergillosis are topical clotrimazole, with a success rate of 80% to 90% with one or more treatments, and oral itraconazole, with a success rate of 60% to 70%. Oral therapy is simpler to administer than topical therapy but is somewhat less successful, requires prolonged treatment, and is relatively expensive. Itraconazole is administered orally at a dose of 5 mg/kg every 12 hours and must be continued for 60 to 90 days or longer. (See Chapter 98 for a complete discussion of this drug.)

Successful topical treatment of aspergillosis was originally documented with enilconazole administered through tubes placed surgically into both frontal sinuses and both sides of the nasal cavity. The drug was administered through the tubes twice daily for 7 to 10 days. Subsequently, it was discovered that the over-the-counter drug clotrimazole was equally efficacious when infused through surgically placed tubes over a 1-hour period. During the 1-hour infusion, the dogs were kept under anesthesia and the caudal nasopharynx and external nares were packed to allow filling of the nasal cavity. It has since been demonstrated that good distribution of the drug can be achieved using a noninvasive technique (discussed in the next paragraphs). Success with clotrimazole using this technique has been similar to that documented with infusion through surgically placed tubes. Debridement of visible fungal plaques during rhinoscopy and before topical therapy appears to increase the rate of success.

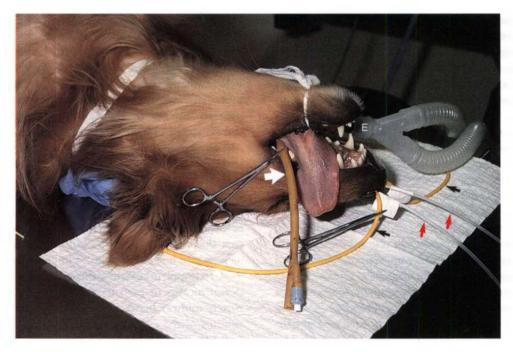
The animal is anesthetized and oxygenated through a cuffed endotracheal tube. The dog is positioned in dorsal recumbency with the nose pulled down parallel with the table (Figs. 15-3 and 15-4). For a large-breed dog, a 24 Fr Foley catheter with a 5-ml balloon is passed through the oral cavity, around the soft palate, and into the caudal nasopharynx such that the bulb is at the junction of the hard and soft palates. The bulb is inflated with approximately 10 ml of air to ensure a snug fit. A laparotomy sponge is inserted within the oropharynx, caudal to the balloon and ventral to the soft palate to help hold the balloon in position and further obstruct the nasal pharynx. Additional laparotomy sponges are packed carefully into the back of the mouth around the tracheal tube to prevent any drug that might leak past the nasopharyngeal packing from reaching the lower airways.

A 10 Fr polypropylene urinary catheter is passed into the dorsal meatus of each nasal cavity to a distance approximately midway between the external naris and the medial canthus of the eye. The correct distance is marked on the catheters with tape to prevent accidentally inserting the catheters too far during the procedure. A 12 Fr Foley catheter with a 5-ml balloon is passed adjacent to the polypropylene catheter into each nasal cavity. The cuff is inflated and pulled snugly against the inside of the naris. A small suture is placed across each naris lateral to the catheter to prevent balloon migration. A gauze sponge is placed between the endotracheal tube and the incisive ducts behind the upper incisors to minimize leakage.

A solution of 1% clotrimazole is administered through the polypropylene catheters. Approximately 30 ml is used for each side in a typical retriever-size dog. Each Foley catheter is checked for filling during the initial infusion and is then clamped when clotrimazole begins to drip from the catheter. The solution is viscous, but excessive pressure is not required for infusion. Additional clotrimazole is administered during the next hour at a rate that results in approximately 1 drop every few seconds from each external naris. In dogs of the size described, a total of approximately 100 to 120 ml will be used.

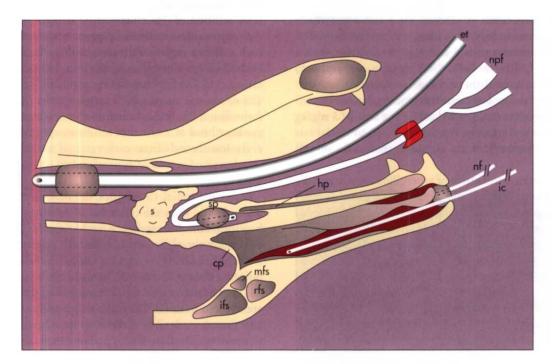
After the initial 15 minutes, the head is tilted slightly to one side and then the other for 15 minutes each and then back into dorsal recumbency for 15 minutes. After this hour of contact time, the dog is rolled into sternal recumbency with the head hanging over the end of the table and the nose pointing toward the floor. The catheters are removed from the external nares, and the clotrimazole and resulting mucus are allowed to drain. Drainage will usually subside in 10 to 15 minutes. A flexible suction tip may be used to expedite this process. The laparotomy pads are then carefully removed from the nasopharynx and oral cavity and counted to ensure that all are retrieved. The catheter in the nasopharynx is removed. Any drug within the oral cavity is swabbed or suctioned.

Two potential complications of clotrimazole treatment are aspiration pneumonia and meningoencephalitis. Meningoencephalitis is generally fatal and results when clotrima-



#### FIG 15-3

Dog with nasal mycotic infection prepared for 1-hour soak with clotrimazole. A cuffed endotracheal tube is in place (E). A 24 Fr Foley catheter (broad arrow) is in the caudal nasopharynx. A 12 Fr Foley catheter (narrow arrows) is obstructing each nostril. A 10 Fr polypropylene catheter (red arrowheads) is placed midway into each dorsal meatus for infusion of the drug. Laparotomy sponges are used to further pack the caudal nasopharynx, around the tracheal tube and the caudal oral cavity.



#### FIG 15-4

Schematic diagram of a cross section of the head of a dog prepared for 1-hour soak with clotrimazole. et, Endotracheal tube; npf, Foley catheter placed in caudal nasopharynx; s, pharyngeal sponges; ic, polypropylene infusion catheter; nf, rostral Foley catheter obstructing nostril; hp, hard palate; sp, soft palate; cp, cribriform plate; rfs, rostral frontal sinus; mfs, medial frontal sinus; lfs, lateral frontal sinus. (Reprinted with permission from Mathews KG et al: Computed tomographic assessment of noninvasive intranasal infusions in dogs with fungal rhinitis, Vet Surg 25:309, 1996.)

zole and its carrier, polyethylene glycol (PEG), make contact with the brain through a compromised cribriform plate. It is difficult to determine the integrity of the cribriform plate before treatment without the aid of computed tomography (CT) or magnetic resonance imaging (MRI), although marked radiographic changes in the caudal nasal cavity should increase concern. Fortunately, complications are not common.

Clinical signs generally resolve in 1 to 2 weeks. A second 1-hour soak is performed if signs persist after 2 weeks. One cause of treatment failure is the inability of clotrimazole to reach all sites of infection. As previously mentioned, removal of fungal plaques with rhinoscopic guidance is thought to improve response to therapy. One or both frontal sinuses are often infected, and it may be necessary to trephine the affected sinus, debulk any fungal granulomas, and directly administer clotrimazole into the sinus. In rare cases, infection extends beyond the nasal cavity (e.g., into the retrobulbar space). Itraconazole treatment is indicated in these patients.

Some clinicians have had success using the combination of itraconazole and another oral antifungal agent, terbinafine, for the treatment of aspergillosis. Published studies are not available (see Chapter 98).

Some dogs have a persistant nasal discharge after treatment for aspergillosis in the absence of identifiable active fungal infection. These dogs may have secondary bacterial rhinitis or sensitivity to inhaled irritants because of the damaged nasal anatomy and mucosa and are managed as described in the section on canine chronic/lymphoplasmacytic rhinitis in this chapter.

#### **Prognosis**

The prognosis for dogs with nasal aspergillosis has improved with the availability of new antifungal agents. For most animals a fair-to-good prognosis is warranted.

#### NASAL PARASITES

#### **NASAL MITES**

Pneumonyssoides caninum is a small white mite approximately 1 mm in size (see Fig. 14-14, A). Most infestations are clinically silent, but some dogs may have moderate-to-severe clinical signs.

#### **Clinical Features and Diagnosis**

A common clinical feature of nasal mites is sneezing, which is often violent. Head shaking, pawing at the nose, reverse sneezing, chronic nasal discharge, and epistaxis can also occur. These signs are similar to those caused by nasal foreign bodies. The diagnosis is made by visualizing the mites during rhinoscopy or by retrograde nasal flushing, as described in Chapter 14. The mites can be easily overlooked in the retrieved saline solution; they should be specifically searched for with slight magnification or by placing dark material behind the specimen for contrast. Further, the mites are

often located in the frontal sinuses and caudal nasal cavity. Marks et al. (1994) report the greatest success in identifying mites by flushing the nasal cavities with halothane in oxygen. The anesthetic mixture causes the mites to migrate to the caudal nasopharynx, where the mites are visualized using an endoscope.

#### **Treatment**

Milbemycin oxime (0.5 to 1 mg/kg, orally, every 7 to 10 days for three treatments) has been used successfully for treating nasal mites. Ivermectin has also been used for treatment (0.2 mg/kg, administered subcutaneously and repeated in 3 weeks), but it is not safe for certain breeds. Any dogs in direct contact with the affected animal should also be treated.

#### **Prognosis**

The prognosis for dogs with nasal mites is excellent.

#### NASAL CAPILLARIASIS

Nasal capillariasis is caused by a nematode, Capillaria (Eucoleus) boehmi, originally identified as a worm of the frontal sinuses in foxes. The adult worm is small, thin, and white and lives on the mucosa of the nasal cavity and frontal sinuses of dogs (see Fig. 14-14, B). The adults shed eggs that are swallowed and pass in the feces. Clinical signs include sneezing and mucopurulent nasal discharge, with or without hemorrhage. The diagnosis is made by identifying double operculated Capillaria (Eucoleus) eggs on routine fecal flotation (similar to the eggs of Capillaria (Eucoleus) aerophila; see Fig. 20-12, C) or visualizing adult worms during rhinoscopy. Treatments include ivermectin (0.2 mg/kg, orally, once) or fenbendazole (25 to 50 mg/kg q12h for 10 to 14 days). Success of treatment should be confirmed with repeated fecal examinations, in addition to resolution of clinical signs. Repeated treatments may be necessary, and reinfection is possible if exposure to contaminated soil continues.

#### NASOPHARYNGEAL POLYPS

Nasopharyngeal polyps are benign growths that occur most often in kittens and young adult cats, although they are occasionally found in older animals. Their origin is unknown, but they are often attached to the base of the eustachian tube. They can extend into the external ear canal, middle ear, pharynx, and nasal cavity. Grossly, they are pink, polypoid growths, often arising from a stalk (Fig. 15-5). Because of their gross appearance, they are sometimes mistaken for neoplasia.

#### **Clinical Features**

Respiratory signs caused by nasopharyngeal polyps include stertorous breathing, upper airway obstruction, and serousto-mucopurulent nasal discharge. Signs of otitis externa or otitis media/interna, such as head tilt, nystagmus, or Horner's syndrome, can also occur.



FIG 15-5

A nasopharyngeal polyp was visualized during rhinoscopy through the exterior naris of a cat with chronic nasal discharge. The polyp was excised by traction and has an obvious stalk.

#### **Diagnosis**

Identification of a soft tissue opacity above the soft palate radiographically and gross visualization of a mass in the nasopharynx, nasal cavity, or external ear canal support a tentative diagnosis of nasopharyngeal polyp. Complete evaluation of cats with polyps also includes a deep otoscopic examination and radiographs or CT scans of the osseous bullae to determine the extent of involvement. The majority of cats with polyps have otitis media, detectable radiographically as thickened bone or increased soft tissue opacity of the bulla (see Fig. 14-6). The definitive diagnosis is made by histopathologic analysis of tissue biopsy; the specimen is usually obtained during surgical excision. Nasopharyngeal polyps are composed of inflammatory tissue, fibrous connective tissue, and epithelium.

#### **Treatment**

Treatment of nasopharyngeal polyps consists of surgical excision. Surgery is usually performed through the oral cavity by traction. In addition, bullae osteotomy should be considered in cats with radiographic or CT evidence of involvement of the osseous bullae. Rarely, rhinotomy is required for complete removal.

An early study by Kapatkin et al. (1990) reported that 5 of 31 cats had regrowth of an excised polyp. Of the five cats with regrowth, four had not had bulla osteotomies. These findings support the importance of addressing involvement of the osseous bulla in cats with polyps. However, a subsequent study by Anderson et al. (2000) reported successful treatment with traction alone, particularly when followed by

a course of prednisolone in some cats. Prednisolone was administered at 1 to 2 mg/kg every 24 hours for 2 weeks, then at half the original dose for 1 week, then every other day for 7 to 10 more days. A course of antibiotics (e.g., amoxicillin) was also administered.

#### **Prognosis**

The prognosis is excellent, but treatment of recurrent disease may be necessary. Regrowth of a polyp can occur at the original site if abnormal tissue remains, with signs of recurrence typically appearing within 1 year. Bulla osteotomies should be considered in cats with recurrence and signs of otitis media if not performed with initial treatment.

#### **NASAL TUMORS**

The majority of nasal tumors in the dog and cat are malignant. Adenocarcinoma, squamous cell carcinoma, and undifferentiated carcinoma are common nasal tumors in dogs. Lymphoma and adenocarcinoma are common in cats. Fibrosarcomas and other sarcomas also occur in both species. Benign tumors include adenomas, fibromas, papillomas, and transmissible venereal tumors (the latter only in dogs).

#### **Clinical Features**

Nasal tumors usually occur in older animals but cannot be excluded from the differential diagnosis of young dogs and cats. No breed predisposition has been consistently identified. Collies and Irish Setters were overrepresented in a report of malignant nasal tumors in dogs by Evans et al. (1989).

The clinical features of nasal tumors (usually chronic) reflect the locally invasive nature of these tumors. Nasal discharge is the most common complaint. The discharge can be serous, mucoid, mucopurulent, or hemorrhagic. One or both nostrils can be involved. With bilateral involvement, the discharge is often worse from one nostril compared with the other. For many animals the discharge is initially unilateral and progresses to bilateral. Sneezing may be reported. Obstruction of the nasal cavity by the tumor may cause decreased or absent air flow through one of the nares.

Deformation of the facial bones, hard palate, or maxillary dental arcade may be visible (see Fig. 13-4). Tumor growth extending into the cranial vault can result in neurologic signs. Growth into the orbit may cause exophthalmos or inability to retropulse the eye. Animals only rarely experience neurologic signs (e.g., seizures, behavior changes, abnormal mental status) or ocular abnormalities as the primary complaints (i.e., no signs of nasal discharge). Weight loss and anorexia may accompany the respiratory signs but are often absent.

#### Diagnosis

A diagnosis of neoplasia is based on clinical features and supported by typical abnormalities detected by imaging of the nasal cavity and frontal sinuses or rhinoscopy. A definitive diagnosis requires histopathologic examination of a biopsy specimen, although fine needle aspirates of nasal masses may provide conclusive results. Imaging (radiography, CT, or MRI) and rhinoscopic abnormalities can reflect soft tissue mass lesions; turbinate, vomer bone, or facial bone destruction (see Figs. 14-2, 14-4, and 14-8, *B*); or diffuse infiltration of the mucosa with neoplastic and inflammatory cells.

Biopsy specimens, including tissue from deep within the lesion, should be obtained in all patients for histologic confirmation. Nasal neoplasms frequently cause a marked inflammatory response of the nasal mucosa and, in some patients, secondary bacterial or fungal infection. A cytologic diagnosis of neoplasia must be accepted cautiously, taking into consideration concurrent inflammation and potentially marked hyperplastic and metaplastic change. Furthermore, in some cases the cytologic characteristics of lymphoma and carcinoma will mimic each other, which may lead to an erroneous classification.

Not all cases of neoplasia will be diagnosed on initial evaluation of the dog or cat. Imaging, rhinoscopy, and biopsy may need to be repeated in 1 to 3 months in animals with persistent signs in which a definitive diagnosis has not been made. CT and MRI are more sensitive techniques for imaging nasal tumors than routine radiography, and one of these should be performed when available (see Fig. 14-8, *B*). Surgical exploration is occasionally necessary to obtain a definitive diagnosis.

Once a definitive diagnosis is made, determining the extent of disease can help in assessing the feasibility of surgical or radiation therapy versus chemotherapy. Some information can be obtained from high-quality nasal radiographs, but CT and MRI are more sensitive methods for evaluating the extent of abnormal tissue. Aspirates of mandibular lymph nodes should be examined cytologically for evidence of local spread. Thoracic radiographs are evaluated, although pulmonary metastases are uncommon at the time of initial diagnosis. Cytologic evaluation of bone marrow aspirates and abdominal radiographs or ultrasound are indicated for patients with lymphoma. Cats with lymphoma are also tested for Fel.V and FIV.

#### **Treatment**

Treatment of benign tumors should include surgical excision. Malignant nasal tumors can be treated with radiation therapy (with or without surgery) and/or chemotherapy. Palliative treatment can also be tried. The treatments of choice for cats with nasal lymphoma are chemotherapy using standard lymphoma protocols (see Chapter 80), radiation therapy, or both. Radiation therapy avoids the systemic adverse effects of chemotherapeutic drugs but may be insufficient if the tumor involves other organs.

Radiation therapy is the treatment of choice for most other malignant nasal tumors. Surgical debulking before radiation is recommended if orthovoltage radiation will be used. Surgery is not beneficial before megavoltage radiation (cobalt or linear accelerator), but improved success of treatment has been recently reported with surgical debulking performed after megavoltage radiotherapy (Adams et al., 2005).

Treatment of malignant nasal tumors with surgery alone does not result in prolonged survival times; it may indeed shorten survival times. It is doubtful that all abnormal tissue can be excised in the majority of cases.

Chemotherapy may be attempted when radiation therapy has failed or is not a viable option. Carcinomas may be responsive to cisplatin, carboplatin, or multiagent chemotherapy. (See Chapter 77 for a discussion of general principles for the selection of chemotherapy.)

Treatment with piroxicam, a nonsteroidal antiinflammatory drug, can be considered for dogs with carcinoma for which radiation therapy is not elected. Partial remissions or improvement in clinical signs have been reported for some dogs with transitional cell carcinoma of the urinary bladder, oral squamous cell carcinoma, and several other carcinomas. Potential side effects include gastrointestinal ulceration (which can be severe) and kidney damage. For dogs with other types of tumors and cats, improvement of clinical signs may be seen with antiinflammatory doses of glucocorticoids. Prednisolone is prescribed for cats, and either prednisone or prednisolone for dogs (0.5 to 1 mg/kg/day; tapered to lowest effective dose). Neither drug should be given in conjunction with piroxicam.

#### **Prognosis**

The prognosis for dogs and cats with untreated malignant nasal tumors is poor. Survival after diagnosis is usually only a few months. Euthanasia is often requested because of persistent epistaxis or discharge, labored respirations, anorexia and weight loss, or neurologic signs. Epistaxis is a poor prognostic indicator. In a study of 132 dogs with untreated nasal carcinoma by Rassnick et al. (2006), the median survival time of dogs with epistaxis was 88 days (95% confidence interval (CI), 65-106 days) and of dogs without epistaxis was 224 days (95% CI, 54-467 days). The overall median survival time was 95 days (range 7-1114 days).

Radiation therapy can prolong survival and improve quality of life in some animals. The therapy is well tolerated by most animals, and in those that achieve remission the quality of life is usually excellent. Studies of dogs treated with megavoltage radiation, with or without prior surgical treatment, by Theon et al. (1993) and Henry et al. (1998) found median survival times of approximately 13 months. Survival rates for 1 and 2 years were 55% to 60% and 25% to 45%, respectively. For dogs receiving megavoltage radiation followed by surgical debulking, median survival time was 47.7 months, with survival rates for 2 and 3 years of 69% and 58%, respectively (Adams et al., 2005). The dogs in the study by Adams et al. (2005) that did not receive postradiotherapy surgery had a median survival of 19.7 months and lower 2- and 3-year survival rates (44% and 24%, respectively).

A study by Evans et al. (1989) of dogs receiving orthovoltage radiation therapy after surgical debulking reported a median survival time of 16.5 months, a 1-year survival rate of 54% and a 2-year survival rate of 43%. Northrup et al. (2001)

report a median survival time of approximately 7 months, a 1-year survival rate of 37%, and a 2-year survival rate of only 17% in dogs treated with surgery and orthovoltage radiation.

Less information is available concerning prognosis in cats. According to Straw et al. (1986), six cats with malignant neoplasms (three with lymphoma) that received radiation therapy had a mean survival time of 19 months. A study by Theon et al. (1994) of 16 cats with nonlymphoid neoplasia receiving radiation therapy showed a 1-year survival rate of 44% and a 2-year survival rate of 17%. Of eight cats with nasal lymphoma treated with cyclophosphamide, vincristine, and prednisolone (COP), six (75%) achieved complete remission (Teske et al., 2002). Median survival time was 358 days, and the estimated 1-year survival rate was 75%. According to preliminary data from Arteaga et al. (2007), cats with nasal lymphoma treated with radiation and chemotherapy had a median survival time of 511 days.

#### ALLERGIC RHINITIS

#### Etiology

Allergic rhinitis has not been well characterized in dogs or cats. However, dermatologists provide anecdotal reports of atopic dogs rubbing the face (possibly indicating nasal pruritus) and experiencing serous nasal discharge, in addition to dermatologic signs. Allergic rhinitis is generally considered to be a hypersensitivity response within the nasal cavity and sinuses to airborne antigens. It is possible that food allergens play a role in some patients. Other antigens are capable of inducing a hypersensitivity response as well, and thus the differential diagnoses must include parasites, other infectious diseases, and neoplasia.

#### **Clinical Features**

Dogs or cats with allergic rhinitis experience sneezing and/or serous or mucopurulent nasal discharge. Signs may be acute or chronic. Careful questioning of the owner may reveal a relationship between signs and potential allergens. For instance, signs may be worse during certain seasons; in the presence of cigarette smoke; or after the introduction of a new brand of kitty litter, new perfumes, cleaning agents, furniture, or fabric in the house. Note that worsening of signs may simply be a result of exposure to irritants rather than an actual allergic response. Debilitation of the animal is not expected.

#### **Diagnosis**

Identifying a historical relationship between signs and a particular allergen and then achieving resolution of signs after removal of the suspected agent from the animal's environment support the diagnosis of allergic rhinitis. When this approach is not possible or successful, a thorough diagnostic evaluation of the nasal cavity is indicated (see Chapters 13 and 14). Nasal radiographs reveal increased soft tissue opacity with minimal or no turbinate destruction. Classically, nasal

biopsy reveals eosinophilic inflammation. It is possible that with chronic disease, a mixed inflammatory response occurs, obscuring the diagnosis. There should be no indication in any of the diagnostic tests of an aggressive disease process, parasites or other active infection, or neoplasia.

#### **Treatment**

Removing the offending allergen from the animal's environment or diet is the ideal treatment of allergic rhinitis. When this is not possible, a beneficial response may be achieved with antihistamines. Chlorpheniramine can be administered orally at a dose of 4 to 8 mg/dog every 8 to 12 hours or 2 mg/cat every 8 to 12 hours. The second-generation antihistamine cetirizine (Zyrtec, Pfizer) may be more successful in cats. A pharmacokinetic study of this drug in healthy cats found a dosage of 1 mg/kg, administered orally every 24 hours, to maintain plasma concentrations similar to those reported in people (Papich et al., 2006). Glucocorticoids may be used if antihistamines are unsuccessful. Prednisone is initiated at a dose of 0.25 mg/kg every 12 hours until signs resolve. The dose is then tapered to the lowest effective amount. If treatment is effective, signs will generally resolve within a few days. Drugs are continued only as long as needed to control signs.

#### **Prognosis**

The prognosis for dogs and cats with allergic rhinitis is excellent if the allergen can be eliminated. Otherwise, the prognosis for control is good, but a cure is unlikely.

#### IDIOPATHIC RHINITIS

Idiopathic rhinitis is a more common diagnosis in cats compared with dogs. The diagnosis cannot be made without a thorough diagnostic evaluation to rule out specific diseases (see Chapters 13 and 14).

#### FELINE CHRONIC RHINOSINUSITIS

#### Etiology

Feline chronic rhinosinusitis has long been presumed to be a result of viral infection with FHV or FCV (see the section on feline upper respiratory infection, p. 223). Persistent viral infection has been implicated, but studies have failed to show an association between tests indicating exposure to or infection with these viruses and clinical signs. It is possible that infection with these viruses results in damaged mucosa that is more susceptible to bacterial infection or that mounts an excessive inflammatory response to irritants or normal nasal flora. Preliminary studies have failed to show an association with feline chronic rhinosinusitis and *Bartonella* infection, based on serum antibody titers or PCR of nasal tissue (Berryessa et al., 2007). In the absence of a known etiology, this disease will be denoted by the term *idiopathic feline chronic rhinosinusitis*.

#### **Clinical Features and Diagnosis**

Chronic mucoid or mucopurulent nasal discharge is the most common clinical sign of idiopathic feline chronic rhinosinusitis. The discharge is typically bilateral. Fresh blood may be seen in the discharge of some cats but is not usually a primary complaint. Sneezing may occur. Given that this is an idiopathic disease, the lack of specific findings is important. Cats should have no funduscopic lesions, no lymphadenopathy, no facial or palate deformities, and healthy teeth and gums. Anorexia and weight loss are rarely reported. Thorough diagnostic testing is indicated, as described in Chapters 13 and 14. Results of such testing do not support the diagnosis of a specific disease. Usual nonspecific findings include turbinate erosion, mucosal inflammation, and increased mucus accumulation as assessed by nasal imaging and rhinoscopy; neutrophilic or mixed inflammation with bacteria on cytology of nasal discharge; and neutrophilic and/or lymphoplasmacytic inflammation on nasal biopsy. Nonspecific abnormalities attributable to chronic inflammation, such as epithelial hyperplasia and fibrosis, may also be seen. Secondary bacterial rhinitis or Mycoplasma infection may be identified.

#### **Treatment**

Cats with idiopathic chronic rhinosinusitis often require management for years. Fortunately, most of these cats are healthy in all other respects. Treatment strategies include facilitating drainage of discharge; decreasing irritants in the environment; controlling secondary bacterial infections; treating possible *Mycoplasmal* or FHV infection; reducing inflammation; and, as a last resort, performing a turbinectomy and frontal sinus ablation (Box 15-1).

Keeping secretions moist, performing intermittent nasal flushes, and judiciously using topical decongestants facilitate drainage. Keeping the cat in a room with a vaporizer, for instance, during the night, can provide symptomatic relief by keeping secretions moist. Alternatively, drops of sterile saline can be placed into the nares. Some cats experience a marked improvement in clinical signs for weeks after flushing of the nasal cavity with copious amounts of saline or dilute betadine solution. General anesthesia is required, and the lower airways must be protected with an endotracheal tube, gauze sponges, and positioning of the head to facilitate drainage from the external nares. Topical decongestants, as described for feline upper respiratory infection (see page 224), may provide symptomatic relief during episodes of severe congestion.

Irritants in the environment can further exacerbate mucosal inflammation. Irritants such as smoke (from tobacco or fireplace) and perfumed products should be avoided. Motivated clients can take steps to improve the air quality in their homes, such as by cleaning the carpet, furniture, drapery, and furnace; regularly replacing air filters; and using an air cleaner. The American Lung Association has a useful Web site with nonproprietary recommendations for improving indoor air quality (www.lungusa.org).



BOX 15-1

Management Considerations for Cats with Idiopathic Chronic Rhinosinusitis

#### Facilitate Drainage of Discharge

Vaporizer treatments
Topical saline administration
Nasal cavity flushes under anesthesia
Topical decongestants

#### Decrease Irritants in the Environment

Improvement of indoor air quality

#### **Control Secondary Bacterial Infections**

Long-term antibiotic treatment

#### Treat Possible Mycoplasma Infection

Antibiotic treatment

#### Treat Possible Herpesvirus Infection

Lysine treatment

#### Reduce Inflammation

Second-generation antihistamine treatment Oral prednisolone treatment

#### Surgical Intervention

Turbinectomy
Frontal sinus ablation

Chronic antibiotic therapy may be required to manage secondary bacterial infections. Broad-spectrum antibiotics such as amoxicillin (22 mg/kg q8-12h) or trimethoprimsulfadiazine (15 mg/kg q12h) are often successful. Chloramphenicol (10 to 15 mg/kg q12h) and doxycycline (5 to 10 mg/kg q12h, followed by a bolus of water) have activity against some bacteria and Chlamydophila and Mycoplasma organisms and can be effective in some cats when other drugs have failed. This author reserves fluoroquinolones for cats with documented resistant gram-negative infections. If a beneficial response to antibiotic therapy is seen within 1 week of its initiation, the antibiotic should be continued for at least 4 to 6 weeks. If a beneficial response is not seen, the antibiotic is discontinued. Note that the frequent stopping and starting of different antibiotics every 7 to 14 days is not recommended and may predispose the cat to resistant gramnegative infections. Cats that respond well during the prolonged course of antibiotics but that relapse shortly after discontinuation of the drug despite 4 to 6 weeks of relief are candidates for continuous long-term antibiotic therapy. Treatment with the previously used antibiotic often can be successfully reinstituted. Amoxicillin administered twice daily is often sufficient.

Treatment with lysine may be effective in cats with active herpesvirus infections. It has been postulated that

excessive concentrations of lysine may antagonize arginine, a promoter of herpesvirus replication. Because the specific organism(s) involved is rarely known, trial therapy is initiated. Lysine (500 mg/cat q12h), which can obtained from health food stores, is added to food. A minimum of 4 weeks is necessary to assess success of treatment.

Anecdotal success in occasional cats has been reported with treatment with the second-generation antihistamine cetirizine (Zyrtec, Pfizer) as described for allergic rhinitis (see p. 232). No efficacy studies are available.

Cats with severe signs that persist despite the previously described methods of supportive care may benefit from glucocorticoids to reduce inflammation. However, certain risks are involved. Glucocorticoids may further predispose the cat to secondary infections, increase viral shedding, and mask signs of a more serious disease. Glucocorticoids should be prescribed only after a complete diagnostic evaluation has been performed to rule out other diseases. Prednisolone is administered at a dose of 0.5 mg/kg every 12 hours. If a beneficial response is seen within 1 week, the dose is gradually decreased to the lowest effective dose. A dose as low as 0.25 mg/kg every 2 to 3 days may be sufficient to control clinical signs. If a clinical response is not seen within 1 week, the drug should be discontinued.

Cats with severe or deteriorating signs that persist despite conscientious care are candidates for turbinectomy and frontal sinus ablation, assuming a complete diagnostic evaluation to eliminate other causes of chronic nasal discharge has been performed (Chapters 13 and 14). Turbinectomy and frontal sinus ablation are difficult surgical procedures. Major blood vessels and the cranial vault must be avoided, and tissue remnants must not be left behind. Anorexia can be a postoperative problem; placement of an esophagostomy or gastrostomy tube (see p. 30) provides an excellent means for meeting nutritional requirements if necessary after surgery. Complete elimination of respiratory signs is unlikely, but signs may be more easily managed. The reader is referred to surgical texts by Fossum or Slatter for a description of the surgical techniques (see Suggested Readings).

#### CANINE CHRONIC/ LYMPHOPLASMACYTIC RHINITIS

#### **Etiology**

Idiopathic chronic rhinitis in dogs is sometimes characterized by the inflammatory infiltrates seen in nasal mucosal biopsies; thus the disease lymphoplasmacytic rhinitis has been described. It was originally reported to be a steroid-responsive disorder (Burgener et al., 1987), but a subsequent report by Windsor et al. (2004) and clinical experience suggest that corticosteroids are not always effective in the treatment of lymphoplasmacytic rhinitis. It is not uncommon for neutrophilic inflammation to be found, predominantly or along with lymphoplasmacytic infiltrates. For these reasons, the less specific term *idiopathic canine chronic rhinitis* will be used.

Many specific causes of nasal disease result in a concurrent inflammatory response because of the disease itself or as a response to the secondary effects of infection or enhanced response to irritants; this makes a thorough diagnostic evaluation of these cases imperative. Windsor et al. (2006) performed multiple PCR assays on paraffin-embedded nasal tissue from dogs with idiopathic chronic rhinitis and failed to find evidence for a role of bacteria (based on DNA load), canine adenovirus-2, parainfluenza virus, *Chlamydophila* spp. or *Bartonella* spp. in affected dogs. High amounts of fungal DNA were found in affected dogs, suggesting a possible contribution to clinical signs. Alternatively, the result may simply reflect decreased clearance of fungal organisms from the diseased nasal cavity.

Although not supported in the previously quoted study, a potential role for *Bartonella* infection has been suggested on the basis of a study that found an association between seropositivity for *Bartonella* spp. and nasal discharge or epistaxis (Henn et al., 2005) and a report of three dogs with epistaxis and evidence of infection with *Bartonella* spp. (Breitschwerdt et al., 2005). A study in our laboratory (Hawkins et al., 2008) failed to find an obvious association between bartonellosis and idiopathic rhinitis, in agreement with findings by Windsor et al. (2006).

#### **Clinical Features and Diagnosis**

The clinical features and diagnosis of idiopathic canine chronic rhinitis are similar to those described for idiopathic feline chronic rhinosinusitis. Chronic mucoid or mucopurulent nasal discharge is the most common clinical sign and is typically bilateral. Fresh blood may be seen in the discharge of some dogs, but it is not usually a primary complaint. Given that it is an idiopathic disease, the lack of specific findings is important. Dogs should have no funduscopic lesions, no lymphadenopathy, no facial or palate deformities, and healthy teeth and gums. Anorexia and weight loss are rarely reported. Thorough diagnostic testing is indicated, as described in Chapters 13 and 14. Results of such testing do not support the diagnosis of a specific disease. Usual nonspecific findings include turbinate erosion, mucosal inflammation, and increased mucus accumulation as assessed by nasal imaging and rhinoscopy; neutrophilic or mixed inflammation with bacteria on cytology of nasal discharge; and lymphoplasmacytic and/or neutrophilic inflammation on nasal biopsy. Nonspecific abnormalities attributable to chronic inflammation, such as epithelial hyperplasia and fibrosis, can also be seen. Secondary bacterial rhinitis or Mycoplasma infection may be identified.

#### **Treatment**

Treatment of idiopathic canine chronic rhinitis is also similar to that described for idiopathic feline rhinosinusitis. Dogs are treated for secondary bacterial rhinitis (as described on p. 233), and efforts are made to decrease irritants in the environment (see p. 233). As with cats, some dogs will benefit from efforts to facilitate the draining of nasal discharge by

humidification of air or instillation of sterile saline into the nasal cavity.

Burgener et al. (1987) reported successful treatment of dogs with lymphoplasmacytic rhinitis using immunosuppressive doses of prednisone (1 mg/kg q12h). A positive response is expected within 2 weeks, at which time the dose of prednisone is decreased gradually to the lowest effective amount. If no response to initial therapy occurs, other immunosuppressive drugs such as azathioprine can be added to the treatment regimen (see Chapter 103). Unfortunately, immunosuppressive treatment is not always effective. If clinical signs worsen during treatment with corticosteroids, the clinician should discontinue therapy and carefully reevaluate the dog for other diseases.

Other treatments that may be effective in some dogs include antihistamines or itraconazole. According to preliminary data from Kuehn (2006), administration of itraconazole (5 mg/kg q12h) resulted in dramatic improvement in clinical signs in some dogs with idiopathic chronic rhinitis. Treatment was required for a minimum of 3 to 6 months. The rationale for this treatment may be supported by the findings of increased fungal load in affected dogs by Windsor et al. (2006).

Dogs with severe or nonresponsive signs are candidates for rhinotomy and turbinectomy, as described for cats on p. 234.

#### **Prognosis**

The prognosis for idiopathic chronic rhinitis in dogs is generally good with respect to management of signs and quality of life. However, some degree of clinical signs persists in many dogs.

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#### CHAPTER OUTLINE

CLINICAL SIGNS

Larynx
Pharynx

DIFFERENTIAL DIAGNOSES FOR LARYNGEAL SIGNS
IN DOGS AND CATS

DIFFERENTIAL DIAGNOSES FOR PHARYNGEAL
SIGNS IN DOGS AND CATS

#### **CLINICAL SIGNS**

#### **LARYNX**

Regardless of the cause, diseases of the larynx result in similar clinical signs, most notably respiratory distress and stridor. Voice change is specific for laryngeal disease but is not always reported. Clients may volunteer that they have noticed a change in their dog's bark or cat's meow, but specific questioning may be necessary to obtain this important information. Localization of disease to the larynx can generally be achieved with a good history and physical examination. A definitive diagnosis is made through a combination of laryngeal radiography, laryngoscopy, and laryngeal biopsy.

Respiratory distress resulting from laryngeal disease is due to airway obstruction. Although most laryngeal diseases are progressive over several weeks to months, animals typically present in acute distress. Dogs and cats are able to compensate for their disease initially through self-imposed exercise restriction. Often an exacerbating event occurs, such as exercise, excitement, or high ambient temperature, resulting in markedly increased respiratory efforts. These increased efforts lead to excess negative pressures on the diseased larynx, sucking the surrounding soft tissues into the lumen, and causing laryngeal inflammation and edema. Obstruction to airflow becomes more severe, leading to even greater respiratory efforts (Fig. 16-1). The airway obstruction can ultimately be fatal.

A characteristic breathing pattern can often be identified on physical examination of patients in distress from extrathoracic (upper) airway obstruction, such as results from laryngeal disease (see Chapter 26). The respiratory rate is normal to only slightly elevated (often 30 to 40 breaths/min), which is particularly remarkable in the presence of overt distress. Inspiratory efforts are prolonged and labored, relative to expiratory efforts. The larynx tends to be sucked into the airway lumen as a result of negative pressure within the extrathoracic airways that occurs during inspiration, making inhalation of air more difficult. During expiration, pressures are positive in the extrathoracic airways, "pushing" the soft tissues open. Nevertheless, expiration may not be effortless. Some obstruction to airflow may occur during expiration with fixed obstructions, such as laryngeal masses. Even with the dynamic obstruction that results from laryngeal paralysis, in which expiration should be possible without any blockage to flow, resultant laryngeal edema and inflammation can interfere with normal expiration. On auscultation, referred upper airway sounds are heard and lung sounds are normal to increased.

Stridor, a high-pitched wheezing sound, is sometimes heard during inspiration. It is audible without a stethoscope, although auscultation of the neck may aid in identifying mild disease. Stridor is produced by air turbulence through the narrowed laryngeal opening. Narrowing of the extrathoracic trachea less commonly produces stridor.

In patients that are not presented for respiratory distress (e.g., for patients with exercise intolerance or voice change), it may be necessary to exercise the patient to identify the characteristic breathing pattern and stridor associated with laryngeal disease.

Some patients with laryngeal disease, particularly whose laryngeal paralysis is an early manifestation of diffuse neuromuscular disease or with distortion of normal laryngeal anatomy, have subclinical aspiration or overt aspiration pneumonia resulting from the loss of normal protective mechanisms. Patients may have clinical signs reflecting aspiration, such as cough, lethargy, anorexia, fever, tachypnea, and abnormal lung sounds. (See p. 309 for a discussion of aspiration pneumonia.)

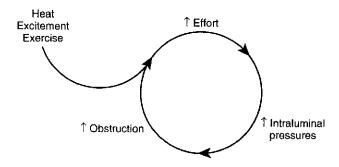


FIG 16-3
Patients with extrathoracic (upper) airway obstruction often present in respiratory distress as a result of a progressive worsening of airway obstruction after an exacerbating

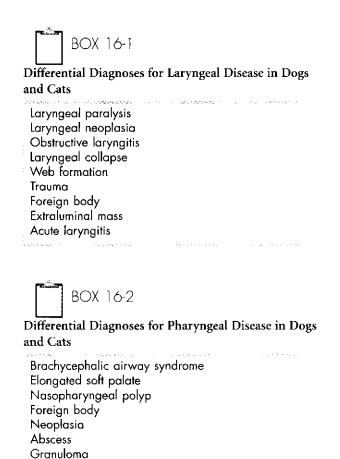
#### **PHARYNX**

Space-occupying lesions of the pharynx can cause signs of upper airway obstruction as described for the larynx, but overt respiratory distress occurs only with advanced disease. More typical presenting signs of pharyngeal disease are stertor, reverse sneezing, gagging, retching, and dysphagia. Stertor is a loud, coarse sound such as that produced by snoring or snorting. Stertor results from excessive soft tissue in the pharynx, such as an elongated soft palate or mass, causing turbulent air flow. Reverse sneezing (see p. 210), gagging, or retching may occur from local stimulation from the tissue itself or from secondary secretions. Dysphagia results from physical obstruction, usually because of a mass. As with laryngeal disorders, a definitive diagnosis is made through a combination of visual examination, radiography, and biopsy of abnormal tissue. Visual examination includes a thorough evaluation of the oral cavity, larynx (see p. 239), and caudal nasopharynx (see p. 215).

# DIFFERENTIAL DIAGNOSES FOR LARYNGEAL SIGNS IN DOGS AND CATS

Differential considerations for dogs and cats with respiratory distress are discussed in Chapter 26.

Dogs are more commonly presented for laryngeal disease than cats and usually have laryngeal paralysis (Box 16-1). Laryngeal neoplasia can occur in dogs or cats. Obstructive laryngitis is a poorly characterized inflammatory disorder. Other possible diseases of the larynx include laryngeal collapse (see p. 241), web formation (i.e., adhesions or fibrotic tissue across the laryngeal opening, usually as a complication of surgery), trauma, foreign body, and compression caused by an extraluminal mass. Acute laryngitis is not a well-characterized disease in dogs or cats but presumably could result from viral or other infectious agents, foreign bodies, or excessive barking.



# DIFFERENTIAL DIAGNOSES FOR PHARYNGEAL SIGNS IN DOGS AND CATS

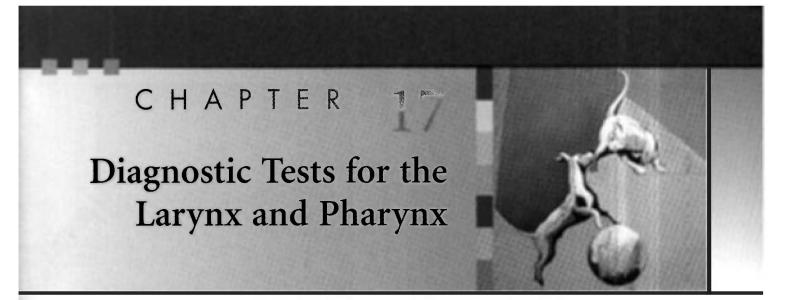
The most common pharyngeal disorders in dogs are brachycephalic airway syndrome and elongated soft palate (Box 16-2). Elongated soft palate is a component of brachycephalic airway syndrome and is discussed with this disorder in Chapter 18 (p. 244), but it can also occur in nonbrachycephalic dogs. The most common pharyngeal disorders in cats are lymphoma and nasopharyngeal polyps (Allen et al., 1999). Nasopharyngeal polyps, nasal tumors, and foreign bodies are discussed in the chapters on nasal diseases (see Chapters 13 to 15). Other differential diagnoses are abscess or granuloma and compression caused by an extraluminal mass.

#### Suggested Readings

Extraluminal mass

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#### CHAPTER OUTLINE

RADIOGRAPHY AND ULTRASONOGRAPHY LARYNGOSCOPY AND PHARYNGOSCOPY

# RADIOGRAPHY AND ULTRASONOGRAPHY

Radiographs of the pharynx and larynx should be evaluated in animals with suspected upper airway disease (Figs. 17-1 and 17-2). They are particularly useful in identifying radiodense foreign bodies such as needles, which can be embedded in tissues and may be difficult to find during laryngoscopy, and adjacent bony changes. Soft tissue masses and soft palate abnormalities may be seen, but apparent abnormal opacities are often misleading, particularly if there is any rotation of the head and neck, and overt abnormalities are often not identified. Abnormal soft tissue opacities or narrowing of the airway lumen identified radiographically must be confirmed withlaryngoscopy or endoscopy and biopsy. Laryngeal paralysis cannot be detected radiographically.

A lateral view of the larynx, caudal nasopharynx, and cranial cervical trachea is usually obtained. The vertebral column interferes with airway evaluation on dorsoventral or ventrodorsal (VD) projections. In animals with abnormal opacities identified on the lateral view, a VD or oblique view may confirm the existence of the abnormality and allow further localization of it. When radiographs of the laryngeal area are obtained, the head is held with the neck slightly extended. Padding under the neck and around the head may be needed to avoid rotation. Radiodense foreign bodies are readily identified. Soft tissue masses that are within the airway or that distort the airway are apparent in some animals with neoplasia, granulomas, abscesses, or polyps, and elongated soft palate is sometimes detectable.

Ultrasonography provides another noninvasive imaging modality for evaluating the pharynx and larynx, and laryngeal motion can be assessed. Because air interferes with sound waves, accurate assessment of this area can be difficult. Nevertheless, ultrasonography was found to be useful in the diagnosis of laryngeal paralysis in dogs (Rudorf et al., 2001). Localization of mass lesions and guidance of needle aspiration can also be performed.

Computed tomography or magnetic resonance imaging can be performed in patients with mass lesions to better determine extent of disease.

# LARYNGOSCOPY AND PHARYNGOSCOPY

Laryngoscopy and pharyngoscopy allow visualization of the larynx and pharynx for assessment of structural abnormalities and laryngeal function. The procedures are indicated in any dog or cat with clinical signs that suggest upper airway obstruction or laryngeal or pharyngeal disease. It should be noted that patients with increased respiratory efforts resulting from upper airway obstruction might have difficulty during recovery from anesthesia. For a period of time between removal of the endotracheal tube and full recovery of neuromuscular function, the patient may be unable to maintain an open airway. Therefore laryngoscopy should not be undertaken in these patients unless the clinician is prepared to perform whatever surgical treatments may be indicated during the same anesthetic period.

The animal is placed in sternal recumbency. Anesthesia is induced and maintained with a short-acting injectable agent without prior sedation. Propofol, sodium thiopental, or sodium thiamylal is commonly used. Depth of anesthesia is carefully titrated, with just enough drug administered to allow visualization of the laryngeal cartilages; some jaw tone is maintained, and spontaneous deep respirations occur. Gauze is passed under the maxilla behind the canine teeth, and the head is elevated by hand or by tying the gauze to a stand (Fig. 17-3). This positioning avoids external compression of the neck. Retraction of the tongue with a gauze sponge should allow visualization of the caudal pharynx and larynx. A laryngoscope is also helpful in illuminating this region and enhancing visualization.



FIG 17-1

Lateral radiograph of the neck, larynx, and pharynx showing normal anatomy. Note that the patient's head and neck are not rotated. Excellent visualization of the soft palate and epiglottis are possible. Images obtained from poorly positioned patients often result in the appearance of "lesions" such as masses or abnormal soft palate because normal structures are captured at an oblique angle or are superimposed on one another.



FIG 17-2 Lateral radiograph of a dog with a neck mass showing marked displacement of the larynx.

The motion of the arytenoid cartilages is evaluated while the patient takes several deep breaths. An assistant is needed to verbally report the onset of each inspiration and expiration by observing chest wall movements. Normally the arytenoid cartilages abduct symmetrically and widely with each



FIG 17-3

Dog positioned with the head held off the table by gauze passed around the maxilla and hung from an intravenous pole. The tongue is pulled out, and a laryngoscope is used to visualize the pharyngeal anatomy and laryngeal motion.

inspiration and close on expiration (Fig. 17-4). Laryngeal paralysis resulting in clinical signs is usually bilateral. The cartilages are not abducted during inspiration. In fact, they may be passively forced outward during expiration and/or sucked inward during inspiration, resulting in paradoxical motion.

If the patient fails to take deep breaths, doxapram hydrochloride (1.1-2.2 mg/kg, administered intravenously) can be given to stimulate breathing. In a study by Tobias et al. (2004), none of the potential systemic side effects of the drug were noted, but some dogs required intubation when increased breathing efforts resulted in significant obstruction to airflow at the larynx.

If no laryngeal motion is observed, examination of the arytenoid cartilages should be continued as long as possible while the animal recovers from anesthesia. Effects of anesthesia and shallow breathing are the most common causes for an erroneous diagnosis of laryngeal paralysis.

After evaluation of laryngeal function, the plane of anesthesia is deepened and the caudal pharynx and larynx are thoroughly evaluated for structural abnormalities, foreign bodies, or mass lesions; appropriate diagnostic samples should be obtained for histopathologic analysis and perhaps culture. The length of the soft palate should be assessed. The soft palate normally extends to the tip of the epiglottis during inhalation. An elongated soft palate can contribute to signs of upper airway obstruction.

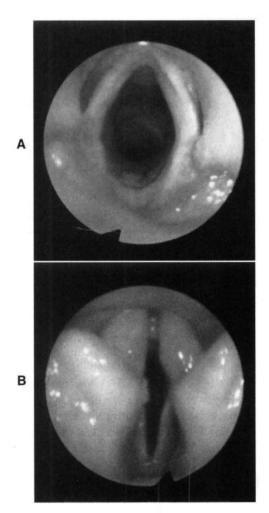


FIG 17-4
Canine larynx. A, During inspiration, arytenoid cartilages and vocal folds are abducted, resulting in wide symmetric opening to trachea. B, During expiration, cartilages and vocal folds nearly close the glottis.

As described in Chapter 14, the caudal nasopharynx should be evaluated for nasopharyngeal polyps, mass lesions, and foreign bodies. Needles or other sharp objects may be buried in tissue, and careful visual examination and palpation are required for detection.

Neoplasia, granulomas, abscesses, or other masses can occur within or external to the larynx or pharynx, causing compression or deviation of normal structures or both. Severe, diffuse thickening of the laryngeal mucosa can be caused by infiltrative neoplasia or obstructive laryngitis. Biopsy specimens for histologic examination should be obtained from any lesions to establish an accurate diagnosis because the prognoses for these diseases are quite different. The normal diverse flora of the pharynx makes culture results difficult or impossible to interpret. Bacterial growth from abscess fluid or tissue obtained from granulomatous lesions may represent infection.

Obliteration of most of the airway lumen by surrounding mucosa is known as *laryngeal collapse*. With prolonged upper airway obstruction, the soft tissues are sucked into the lumen by the increased negative pressure created as the dog or cat struggles to get air into its lungs. Eversion of the laryngeal saccules, thickening and elongation of the soft palate, and inflammation with thickening of the pharyngeal mucosa can occur. The laryngeal cartilages can become soft and deformed, unable to support the soft tissues of the pharynx. It is unclear whether this chondromalacia is a concurrent or secondary component of laryngeal collapse. Collapse most often occurs in dogs with brachycephalic airway syndrome but can also occur with any chronic obstructive disorder.

The trachea should be examined radiographically or visually with an endoscope if abnormalities are not identified on laryngoscopy in the dog or cat with signs of upper airway obstruction. For these animals, the laryngeal cartilages can be held open with an endotracheal tube for a cursory examination of the proximal trachea at the time of laryngoscopy if an endoscope is not available.

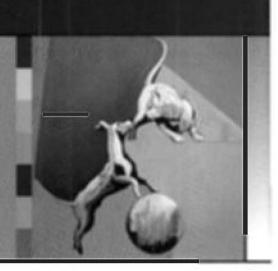
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Tobias KM et al: Effects of doxapram HCl on laryngeal function of normal dogs and dogs with naturally occurring laryngeal paralysis, *Vet Anaesthesia and Analgesia* 31:258, 2004.

# CHAPTER

# Disorders of the Larynx and Pharynx



#### CHAPTER OUTLINE

LARYNGEAL PARALYSIS
BRACHYCEPHALIC AIRWAY SYNDROME
OBSTRUCTIVE LARYNGITIS
LARYNGEAL NEOPLASIA

#### LARYNGEAL PARALYSIS

Laryngeal paralysis refers to a failure of the arytenoid cartilages to abduct during inspiration, creating extrathoracic (upper) airway obstruction. The abductor muscles are innervated by the left and right recurrent laryngeal nerves. If clinical signs develop, both arytenoid cartilages are usually affected.

#### Etiology

Potential causes of laryngeal paralysis are listed in Box 18-1. Laryngeal paralysis is most often idiopathic. Trauma or neoplasia involving the ventral neck can damage the recurrent laryngeal nerves directly or through inflammation and scarring. Masses or trauma involving the anterior thoracic cavity can also cause damage to the recurrent laryngeal nerves as they course around the subclavian artery (right side) or ligamentum arteriosum (left side). Dogs with polyneuropathy-polymyopathy can be presented with laryngeal paralysis as the predominant clinical sign. Polyneuropathies in turn have been associated with immune-mediated diseases, endocrinopathies, or other systemic disorders (see Chapter 71). Congenital laryngeal paralysis has been documented in the Bouvier des Flandres and is suspected in Siberian Huskies and Bull Terriers. A laryngeal paralysis-polyneuropathy complex has been described in young Dalmations, Rottweilers, and Great Pyrenees. Anecdotally, there may be an increasing incidence of idiopathic laryngeal paralysis in older Golden and Labrador Retrievers, and in one study 47 of 140 dogs (34%) with laryngeal paralysis were Labrador Retrievers (MacPhail et al., 2001). Laryngeal paralysis is uncommon in cats.

#### **Clinical Features**

Laryngeal paralysis can occur at any age and in any breed, although the idiopathic form is most commonly seen in older large-breed dogs. Clinical signs of respiratory distress and stridor are a direct result of narrowing of the airway at the arytenoid cartilages and vocal folds. The owner may also note a change in voice (i.e., bark or meow). Most patients are presented for acute respiratory distress, in spite of the chronic, progressive nature of this disease. Decompensation is frequently a result of exercise, excitement, or high environmental temperatures, resulting in a cycle of increased respi-



BOX 18-1

Potential Causes of Laryngeal Paralysis

#### Idiopathic

#### **Ventral Cervical Lesion**

Trauma to nerves

Direct trauma

Inflammation

**Fibrosis** 

Neoplasia

Other inflammatory or mass lesion

#### **Anterior Thoracic Lesion**

Neoplasia

Trauma

Postoperative

Other

Other inflammatory or mass lesion

#### Polyneuropathy and Polymyopathy

Idiopathic

Immune mediated

Endocrinopathy

Hypothyroidism

Other systemic disorder

Toxicity

Congenital disease

Myasthenia gravis

ratory efforts; increased negative airway pressures, which suck the soft tissue into the airway; and pharyngeal edema and inflammation, which lead to further increased respiratory efforts. Cyanosis, syncope, and death can occur. Dogs with respiratory distress require immediate emergency therapy.

Some dogs with laryngeal paralysis exhibit gagging or coughing with eating or have overt aspiration pneumonia, presumably resulting from concurrent pharyngeal dysfunction or a more generalized polyneuropathy-polymyopathy.

#### Diagnosis

A definitive diagnosis of laryngeal paralysis is made through laryngoscopy (see p. 239). Movement of the arytenoid cartilages is observed during a light plane of anesthesia while the patient is taking deep breaths. In laryngeal paralysis the arytenoid cartilages and vocal folds remain closed during inspiration and open slightly during expiration. The larynx does not exhibit the normal coordinated movement associated with breathing, opening on inspiration and closing on expiration. Additional laryngoscopic findings may include pharyngeal edema and inflammation. The larynx and pharynx are also examined for neoplasia, foreign bodies, or other diseases that might interfere with normal function and for laryngeal collapse (see p. 241).

Once a diagnosis of laryngeal paralysis is established, additional diagnostic tests should be considered to identify underlying or associated diseases, to rule out concurrent pulmonary problems (e.g., aspiration pneumonia) that may be contributing to the clinical signs, and to rule out concurrent pharyngeal and esophageal motility problems (Box 18-2). The latter is especially important if surgical correction for the treatment of laryngeal paralysis is being considered. If the diagnostic tests fail to identify a cause, idiopathic laryngeal paralysis is diagnosed.

#### **Treatment**

In animals with respiratory distress, emergency medical therapy to relieve upper airway obstruction is indicated (see Chapter 26). Following stabilization and a thorough diagnostic evaluation, surgery is usually the treatment of choice. Even when specific therapy can be directed at an associated disease (e.g., hypothyroidism), complete resolution of clinical signs of laryngeal paralysis is rarely seen. Also, most cases are idiopathic, and signs are generally progressive.

Various laryngoplasty techniques have been described, including arytenoid lateralization (tie-back) procedures, partial laryngectomy, and castellated laryngoplasty. The goal of surgery is to provide an adequate opening for the flow of air but not one so large that the animal is predisposed to aspiration and the development of pneumonia. Several operations to gradually enlarge the glottis may be necessary to minimize the chance of subsequent aspiration. The recommended initial procedure for most dogs and cats is unilateral arytenoid lateralization.

If surgery is not an option, medical management consisting of antiinflammatory doses of short-acting glucocorti-



BOX 18-2

Diagnostic Evaluation of Dogs and Cats with Confirmed Laryngeal Paralysis

#### **Underlying Cause**

Thoracic radiographs
Cervical radiographs
Serum biochemical panel
Thyroid hormone evaluation
Ancillary tests in select cases

Evaluation for polyneuropathy-polymyopathy

- Electromyography
- Nerve conduction measurements
   Antinuclear antibody test
   Antiacetylcholine receptor antibody test

#### **Concurrent Pulmonary Disease**

Thoracic radiographs

#### **Concurrent Pharyngeal Dysfunction**

Evaluation of gag reflex
Observation of patient swallowing food and water
Fluoroscopic observation of barium swallow

#### **Concurrent Esophageal Dysfunction**

Thoracic radiographs
Contrast-enhanced esophagram
Fluoroscopic observation of barium swallow

coids (e.g., prednisone, 0.5 mg/kg given orally q12h initially) and cage rest may reduce secondary inflammation and edema of the pharynx and larynx and enhance airflow.

#### **Prognosis**

The overall prognosis for dogs with laryngeal paralysis treated surgically is fair to good. As many as 90% of owners of dogs with laryngeal paralysis that underwent unilateral arytenoid lateralization consider the procedure successful I year or longer after surgery (White, 1989; Hammel et al., 2006). MacPhail et al. (2001) reported a median survival time of 1800 days (nearly 5 years) for 140 dogs that underwent various surgical procedures, although the mortality rate from postoperative complications was high at 14%. The most common complication is aspiration pneumonia. A guarded prognosis is warranted for patients with signs of aspiration, dysphagia, megaesophagus, or systemic polyneuropathy or polymyopathy. Dogs with laryngeal paralysis as an early manifestation of generalized polyneuropathy or polymyopathy may have progression of signs.

#### BRACHYCEPHALIC AIRWAY SYNDROME

The term brachycephalic airway syndrome, or upper airway obstruction syndrome, refers to the multiple anatomic abnor-

В





FIG 18-1
Two Bulldog puppies (A) and a Boston Terrier (B) with brachycephalic airway syndrome. Abnormalities can include stenotic nares, elongated soft palate, everted laryngeal saccules, laryngeal collapse, and hypoplastic trachea.

malities commonly found in brachycephalic dogs and, to a lesser extent, in short-faced cats such as Himalayans. The predominant anatomic abnormalities include stenotic nares, elongated soft palate, and, in Bulldogs, hypoplastic trachea. Prolonged upper airway obstruction resulting in increased inspiratory efforts may lead to eversion of the laryngeal saccules and, ultimately, laryngeal collapse. The severity of these abnormalities varies, and one or any combination of these abnormalities may be present in any given brachycephalic dog or short-faced cat (Fig. 18-1).

Concurrent gastrointestinal signs such as ptyalism, regurgitation, and vomiting are common in dogs with brachycephalic airway syndrome (Poncet et al., 2005) Underlying gastrointestinal disease may be a concurrent problem in these breeds of dogs or may result from or be exacerbated by the increased intrathoracic pressures generated in response to the upper airway obstruction.

#### **Clinical Features**

The abnormalities associated with the brachycephalic airway syndrome impair the flow of air through the extrathoracic (upper) airways and cause clinical signs of upper airway obstruction, including loud breathing sounds, stertor, increased inspiratory efforts, cyanosis, and syncope. Clinical signs are exacerbated by exercise, excitement, and high environmental temperatures. The increased inspiratory effort commonly associated with this syndrome may cause secondary edema and inflammation of the laryngeal and pharyngeal mucosae and enhance eversion of the laryngeal saccules or laryngeal collapse, further narrowing the glottis, exacerbating the clinical signs, and creating a vicious cycle. As a result, some dogs may be presented with life-threatening upper airway obstruction that requires immediate emergency therapy. Concurrent gastrointestinal signs are commonly reported.

#### **Diagnosis**

A tentative diagnosis is made on the basis of the breed, clinical signs, and the appearance of the external nares (Fig. 18-2). Stenotic nares are generally bilaterally symmetric, and the alar folds may be sucked inward during inspiration, thereby worsening the obstruction to airflow. Laryngoscopy (see Chapter 17) and radiographic evaluation of the trachea (see Chapter 20) are necessary to fully assess the extent and severity of abnormalities. Most other causes of upper airway obstruction (see Chapter 26, and Boxes 16-1 and 16-2) can also be ruled in or out on the basis of the results of these diagnostic tests.

#### **Treatment**

Therapy should be designed to enhance the passage of air through the upper airways and to minimize the factors that exacerbate the clinical signs (e.g., excessive exercise and excitement, overheating). Surgical correction of the anatomic defects is the treatment of choice. The specific surgical procedure selected depends on the nature of the existing problems and can include widening of the external nares and removal of excessive soft palate and everted laryngeal saccules.

Correction of stenotic nares is a simple procedure and can lead to a surprising alleviation of the signs in affected patients. Stenotic nares can be safely corrected at 3 to 4 months of age, *ideally before clinical signs develop*. The soft palate should be evaluated at the same time and also corrected if elongated. Such early relief of obstruction should decrease the amount of negative pressure placed on the pharyngeal and laryngeal structures during inspiration and decrease progression of disease.

Medical management consisting of the administration of short-acting glucocorticoids (e.g., prednisone, 0.5 mg/kg given orally q12h initially) and cage rest may reduce the secondary inflammation and edema of the pharynx and larynx and enhance airflow, but it will not eliminate the problem. Emergency therapy may be required to alleviate the upper airway obstruction in animals presenting in respiratory distress (see Chapter 26).

Weight management and concurrent treatment for gastrointestinal disease should not be neglected in patients with brachycephalic airway syndrome.

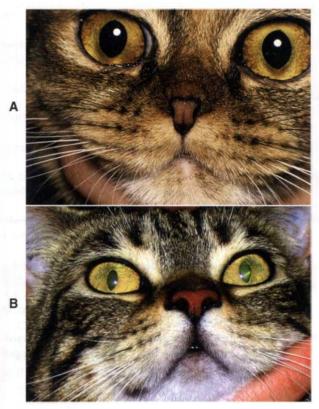


FIG 18-2
Cat with severely stenotic nares (A), as compared with the nares of a normal cat (B). Early correction of stenotic nares and other amenable upper airway obstructions, such as an elongated soft palate, is highly recommended.

#### **Prognosis**

The prognosis depends on the severity of the abnormalities at the time of diagnosis and the ability to surgically correct them. The clinical signs will progressively worsen if the underlying problems go uncorrected. The prognosis after early surgical correction of the abnormalities is good for many animals. Laryngeal collapse (see p. 241) is generally considered a poor prognostic indicator, although a recent study demonstrated that even dogs with severe laryngeal collapse can respond well to surgical intervention (Torrez et al., 2006). Permanent tracheostomy can be considered as a salvage procedure in animals with severe collapse that are not responsive. A hypoplastic trachea is not surgically correctable, but there is no clear relationship between the degree of hypoplasia and morbidity or mortality.

#### **OBSTRUCTIVE LARYNGITIS**

Nonneoplastic infiltration of the larynx with inflammatory cells can occur in dogs and cats, causing irregular proliferation, hyperemia, and swelling of the larynx. Clinical signs of an upper airway obstruction result. The larynx may appear grossly neoplastic during laryngoscopy

but is differentiated from neoplasia on the basis of the histopathologic evaluation of biopsy specimens. Inflammatory infiltrates can be granulomatous, pyogranulomatous, or lymphocytic-plasmacytic. Etiologic agents have not been identified.

This syndrome is poorly characterized and probably includes several different diseases. Some animals respond to glucocorticoid therapy. Prednisone or prednisolone (1.0 mg/kg given orally q12h) is used initially. Once the clinical signs have resolved, the dose of prednisone can be tapered to the lowest amount that effectively maintains remission of clinical signs. Conservative excision of the tissue obstructing the airway may be necessary in animals with severe signs of upper airway obstruction or large granulomatous masses.

The prognosis varies, depending on the size of the lesion, the severity of laryngeal damage, and the responsiveness of the lesion to glucocorticoid therapy.

#### LARYNGEAL NEOPLASIA

Neoplasms originating from the larynx are uncommon in dogs and cats. More commonly, tumors originating in tissues adjacent to the larynx, such as thyroid carcinoma and lymphoma, compress or invade the larynx and distort normal laryngeal structures. Clinical signs of extrathoracic (upper) airway obstruction result. Laryngeal tumors include carcinoma (squamous cell, undifferentiated, and adenocarcinoma), lymphoma, melanoma, mast cell tumors and other sarcomas, and benign neoplasia. Lymphoma is the most common tumor in cats.

#### **Clinical Features**

The clinical signs of laryngeal neoplasia are similar to those of other laryngeal diseases and include noisy respiration, stridor, increased inspiratory efforts, cyanosis, syncope, and a change in bark or meow. Mass lesions can also cause concurrent dysphagia, aspiration pneumonia, or visible or palpable masses in the ventral neck.

#### **Diagnosis**

Extralaryngeal mass lesions are often identified by palpation of the neck. Primary laryngeal tumors are rarely palpable and are best identified by laryngoscopy. Laryngeal radiographs, ultrasonography, or computed tomography can be useful in assessing the extent of disease. Differential diagnoses include obstructive laryngitis, nasopharyngeal polyp, foreign body, traumatic granuloma, and abscess. For a definitive diagnosis of neoplasia to be made, histologic examination of a biopsy specimen of the mass must be done. A diagnosis of malignant neoplasia should not be made on the basis of the gross appearance alone.

#### **Treatment**

The therapy used depends on the type of tumor identified histologically. Benign tumors should be excised surgically, if possible. Complete surgical excision of malignant tumors is rarely possible, although ventilation may be improved and time may be gained to allow other treatments such as radiation or chemotherapy to become effective. Complete laryngectomy and permanent tracheostomy may be considered in select animals.

#### **Prognosis**

The prognosis in animals with benign tumors is excellent if the tumors can be totally resected. Malignant neoplasms are associated with a poor prognosis.

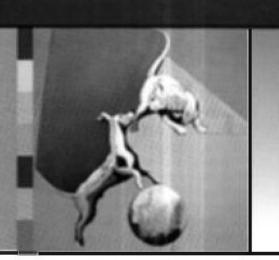
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# CHAPTER 19

# Clinical Manifestations of Lower Respiratory Tract Disorders



#### CHAPTER OUTLINE

**CLINICAL SIGNS** 

Cough

Exercise Intolerance and Respiratory Distress
DIAGNOSTIC APPROACH TO DOGS AND CATS
WITH LOWER RESPIRATORY TRACT DISEASE

Initial Diagnostic Evaluation

Pulmonary Specimens and Specific Disease Testing

#### **CLINICAL SIGNS**

In this discussion, the term lower respiratory tract disorders refers to diseases of the trachea, bronchi, bronchioles, alveoli, interstitium, and vasculature of the lung (Box 19-1). Dogs and cats with diseases of the lower respiratory tract are commonly seen for evaluation of cough. Lower respiratory tract diseases that interfere with the oxygenation of blood can result in respiratory distress, exercise intolerance, weakness, cyanosis, or syncope. Nonlocalizing signs such as fever, anorexia, weight loss, and depression also occur and are the only presenting sign in some animals. In rare instances, potentially misleading signs, such as vomiting, can occur in animals with lower respiratory tract disease. Auscultation and thoracic radiography help localize the disease to the lower respiratory tract in these animals. The two major presenting signs in animals with lower respiratory tract disease, cough and respiratory distress, can be further characterized by a careful history and physical examination.

#### COUGH

A cough is an explosive release of air from the lungs through the mouth. It is generally a protective reflex to expel material from the airways, although inflammation or compression of the airways can also stimulate cough. Cough is sometimes caused by disease outside of the lower respiratory tract. Chylothorax can cause cough. Although not well documented in dogs or cats, gastroesophageal reflux and postnasal drip are common causes of cough in people.

Classically, differential diagnoses for cough are divided into those that cause productive cough and those that cause nonproductive cough. A productive cough results in the delivery of mucus, exudate, edema fluid, or blood from the airways into the oral cavity. A moist sound can often be heard during the cough. Animals rarely expectorate the fluid, but swallowing can be seen after a coughing episode. If expectoration occurs, clients may confuse the cough with vomiting. In human medicine, categorizing cough as productive or nonproductive is rarely difficult because the patient can report the coughing up of secretions. In veterinary medicine, recognition of a productive cough is more difficult. If the owner or veterinarian has heard or seen evidence that the cough is productive, it usually is. However, not hearing or seeing evidence of productivity does not rule out the possibility of its presence. Productive coughs are most commonly caused by inflammatory or infectious diseases of the airways or alveoli and by heart failure (Box 19-2).

Hemoptysis is the coughing up of blood. Blood-tinged saliva may be observed within the oral cavity or dripping from the commissures of the mouth after a cough. Hemoptysis is an unusual clinical sign that most commonly occurs in animals with heartworm disease or pulmonary neoplasia. Less common causes of hemoptysis are mycotic infections, foreign bodies, severe congestive heart failure, thromboembolic disease, lung lobe torsion, and some systemic bleeding disorders such as disseminated intravascular coagulation (see Box 19-2).

Intensity of cough is useful in prioritizing the differential diagnoses. Cough associated with airway inflammation (i.e., bronchitis) or large airway collapse is often loud, harsh, and paroxysmal. The cough associated with tracheal collapse is often described as a "goose-honk." Cough resulting from tracheal disease can usually be induced by palpation of the trachea, although the concurrent involvement of deeper airways is possible. Cough associated with pneumonias and pulmonary edema is usually soft.

The association of coughing with temporal events can be helpful. Cough resulting from tracheal disease is exacerbated by pressure on the neck, such as pulling on the animal's collar. Cough caused by heart failure tends to occur more



Differential Diagnoses for Lower Respiratory Tract Disease in Dogs and Cats

#### Disorders of the Trachea and Bronchi

Canine infectious tracheobronchitis Canine chronic bronchitis

Collapsing trachea

Feline bronchitis (idiopathic)

Allergic bronchitis

Bacterial and Mycoplasmal infections

Oslerus osleri infection

Neoplasia

Foreign body

Tracheal tear

Bronchial compression

Left atrial enlargement

Hilar lymphadenopathy

Neoplasia

#### Disorders of the Pulmonary Parenchyma and Vasculature

Infectious diseases

Viral pneumonias

- Canine influenza
- Canine distemper
- Calicivirus
- Feline infectious peritonitis

Bacterial pneumonia Protozoal pneumonia

Toxoplasmosis

Fungal pneumonia

- Blastomycosis
- Histoplasmosis
- Coccidioidomycosis

Parasitic disease

- Heartworm disease
- Pulmonary parasites
  - Paragonimus infection
  - Aelurostrongylus infection
  - Capillaria infection
  - Crenosoma infection

Aspiration pneumonia

Eosinophilic lung disease

Idiopathic interstitial pneumonias

Idiopathic pulmonary fibrosis

Pulmonary neoplasia

Pulmonary contusions

Pulmonary hypertension

Pulmonary thromboembolism

Pulmonary edema

frequently at night, whereas cough caused by airway inflammation (bronchitis) tends to occur more frequently upon rising from sleep or during and after exercise or exposure to cold air. The client's perception of frequency may be biased by the times of day during which they have the most contact with their pets, often in the evenings and during exercise.

Surprisingly, cats with many of the disorders listed in Box 19-2 do not cough. In cats that cough, the index of suspicion for bronchitis, lung parasites, and heartworm disease is high.

### EXERCISE INTOLERANCE AND RESPIRATORY DISTRESS

Diseases of the lower respiratory tract can compromise the lung's function of oxygenating the blood through a variety of mechanisms (see the section on blood gas analysis in Chapter 20). Clinical signs of such compromise begin as mildly increased respirations and subtly decreased activity and progress through exercise intolerance (manifested as reluctance to exercise or respiratory distress with exertion) to overt respiratory distress at rest. Because of compensatory mechanisms, the ability of most pets to self-regulate their activity, and the inability of pets to communicate, many veterinary patients with compromised lung function arrive in overt respiratory distress. Dogs in overt distress will often stand with their neck extended and elbows abducted. Movements of the abdominal muscles may be exaggerated. Healthy

cats have minimally visible respiratory efforts. Cats that show noticeable chest excursions or open-mouth breathing are severely compromised. Patients in overt distress require rapid physical assessment and immediate stabilization before further diagnostic testing, as discussed in Chapter 26.

#### Resting Respiratory Rate

Resting respiratory rate can be used as an indicator of pulmonary function in patients that are not yet in respiratory distress. The measurement is ideally made at home by the owner, which spares the patient the stress of the veterinary hospital. The normal respiratory rate of a dog or cat without stress, at rest, is less than 20 respirations per minute. A rate of up to 30 respirations per minute is generally considered normal during a routine physical examination.

#### **Mucous Membrane Color**

Cyanosis, in which normally pink mucous membranes are bluish, is a sign of severe hypoxemia and indicates that the increased respiratory effort is not sufficiently compensating for the degree of respiratory dysfunction. Pallor of mucous membranes is a more common sign of acute hypoxemia resulting from respiratory disease.

#### **Breathing Pattern**

Patients in respiratory distress resulting from diseases of the lower respiratory tract, excluding the large airways, typically



Differential Diagnoses for Productive Cough\* in Dogs and Cats

#### Edema

Heart failure Noncardiogenic pulmonary edema

#### **Mucus or Exudate**

Canine infectious tracheobronchitis Canine chronic bronchitis Feline bronchitis (idiopathic)<sup>†</sup> Allergic bronchitis<sup>†</sup> Bacterial infection (bronchitis or pneumonia) Parasitic disease<sup>†</sup> Aspiration pneumonia Fungal pneumonia (severe)

#### **Blood** (Hemoptysis)

Heartworm disease<sup>†</sup>
Neoplasia
Fungal pneumonia
Thromboembolism
Severe heart failure
Foreign body
Lung lobe torsion
Systemic bleeding disorder

have rapid and often shallow respirations; increased expiratory or inspiratory efforts, or both; and abnormal lung sounds on auscultation. Patients with intrathoracic large airway obstruction (intrathoracic trachea and/or large bronchi) generally have normal to slightly increased respiratory rate; prolonged, labored expiration; and audible or auscultable expiratory sounds (see Chapter 26).

#### DIAGNOSTIC APPROACH TO DOGS AND CATS WITH LOWER RESPIRATORY TRACT DISEASE

#### INITIAL DIAGNOSTIC EVALUATION

The initial diagnostic evaluation of dogs or cats with signs of lower respiratory tract disease includes a complete history, physical examination, thoracic radiographs, and complete blood count (CBC). Further diagnostic tests are selected on the basis of information obtained from these procedures; these include the evaluation of specimens collected from the lower respiratory tract, tests for specific diseases, and arterial blood gas analysis. Historical information was discussed in previous paragraphs.

#### Physical Examination

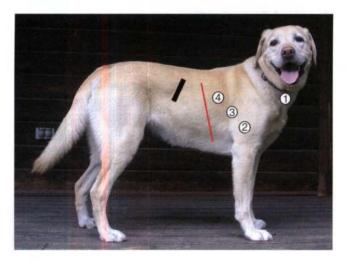
Measurement of respiratory rate, assessment of mucous membrane color, and observation of the breathing pattern were described in the previous sections. A complete physical examination, including a fundic examination, is warranted to identify signs of disease that may be concurrently or secondarily affecting the lungs (e.g., systemic mycoses, metastatic neoplasia, megaesophagus). The cardiovascular system should be carefully evaluated. Mitral insufficiency murmurs are frequently auscultated in older small-breed dogs brought to the clinician with the primary complaint of cough. Mitral insufficiency is often an incidental finding, but the clinician must consider both cardiac and respiratory tract diseases as differential diagnoses in these animals. Mitral insufficiency can lead to left atrial enlargement with compression of the mainstem bronchi, causing cough, or to congestive heart failure. Dogs in congestive heart failure are nearly always tachycardic, and any cough is usually soft. Other signs of heart disease include prolonged capillary refill time, weak or irregular pulses, abnormal jugular pulses, ascites or subcutaneous edema, gallop rhythms, and pulse deficits. Thoracic radiographs and occasionally echocardiography may be needed before cardiac problems can be comfortably ruled out as a cause of lower respiratory tract signs.

**Thoracic auscultation.** Careful auscultation of the upper airways and lungs is a critical component of the physical examination in dogs and cats with respiratory tract signs. Auscultation should be performed in a quiet location with the animal calm. Panting and purring do not result in deep inspiration, precluding evaluation of lung sounds. The heart and upper airways should be auscultated first. The clinician can then mentally subtract the contribution of these sounds from the sounds auscultated over the lung fields.

Initially, the stethoscope is placed over the trachea near the larynx (Fig. 19-1). Discontinuous snoring or snorting sounds can be referred from the nasal cavity and pharynx as a result of obstructions stemming from structural abnormalities, such as an elongated soft palate or mass lesions, and excessive mucus or exudate. Wheezes, which are continuous high-pitched sounds, occur in animals with obstructive laryngeal conditions, such as laryngeal paralysis, neoplasia, inflammation, and foreign bodies. Discontinuous snoring sounds and wheezes are known as stertor and stridor, respectively, when they can be heard without a stethoscope. The entire cervical trachea is then auscultated for areas of highpitched sounds caused by localized airway narrowing. Several breaths are auscultated with the stethoscope in each position, and the phase of respiration in which abnormal sounds occur is noted. Abnormal sounds resulting from extrathoracic disease are generally loudest during inspiration.

The lungs are auscultated next. Normally, the lungs extend cranially to the thoracic inlet and caudally to about the seventh rib ventrally along the sternum and to approximately the ninth intercostal space dorsally along the spine (see Fig. 19-1). The cranioventral, central, and dorsal lung fields on both the left and right sides are auscultated systematically.

<sup>\*</sup>Because it can be difficult to determine the productive nature of a cough in veterinary medicine, these differential diagnoses should also be considered in patients with nonproductive cough. †Diseases of the lower respiratory tract disease most often associated with cough in cats. Cough in cats is rarely identified as productive.



#### FIG 19-1

Auscultation of the respiratory tract begins with the stethoscope positioned over the trachea (stethoscope position 1). After assessing upper airway sounds, the stethoscope is positioned to evaluate the cranioventral, central, and dorsal lung fields on both sides of the chest (stethoscope positions 2), 3, and 4). Note that the lung fields extend from the thoracic inlet to approximately the seventh rib along the sternum and to approximately the ninth intercostal space along the spine (thin red line). Common mistakes are to neglect the cranioventral lung fields, reached by placing the stethoscope between the forelimb and the chest, and to position the stethoscope too far caudally, beyond the lung fields and over the liver. (Thick black line indicates position of the thirteenth rib.)

Any asymmetry in the sounds between the left and right sides is abnormal.

Normal lung sounds have been described historically as a mixture of "bronchial" and "vesicular" sounds, although all sounds originate from the large airways. The bronchial sounds are most prominent in the central regions of the lungs. They are tubular sounds similar in character to those heard over the trachea, but they are quieter. Vesicular sounds are most prominent in the peripheral lung fields. They are soft and have been likened to a breeze blowing through leaves. These normal sounds are best described as "normal breath sounds."

Decreased lung sounds over one or both sides of the thorax occur in dogs and cats with pleural effusion, pneumothorax, diaphragmatic hernia, or mass lesions. Surprisingly, consolidated lung lobes and mass lesions can result in enhanced lung sounds because of the improved transmission of airway sounds from adjacent lobes. Abnormal lungs sounds are described as increased breath sounds (alternatively, harsh lung sounds), crackles, or wheezes. Increased breath sounds are a nonspecific finding but are common in patients with pulmonary edema or pneumonia. Crackles are nonmusical, discontinuous noises that sound like paper being crumpled or bubbles popping. Diseases resulting in the formation of edema or an exudate within the airways (e.g., pulmonary edema, infectious or aspiration pneumo-

nia, bronchitis) and some interstitial pneumonias, particularly interstitial fibrosis, can result in crackles. Wheezes are musical, continuous sounds that indicate the presence of airway narrowing. Narrowing can occur as a result of bronchoconstriction, bronchial wall thickening, exudate or fluid within the bronchial lumen, intraluminal masses, or external airway compression. They are most commonly heard in cats with bronchitis. Wheezes caused by an intrathoracic airway obstruction are loudest during early expiration. Sudden snapping at the end of expiration can be heard in some dogs with intrathoracic tracheal collapse.

#### Radiography

Thoracic radiographs are indicated in dogs and cats with lower respiratory tract signs. Neck radiographs should also be obtained in animals with suspected tracheal disease. Radiography is perhaps the single most helpful diagnostic tool in the evaluation of dogs and cats with intrathoracic disease. It helps in localizing the problem to an organ system (i.e., cardiac, pulmonary, mediastinal, pleural), identifying the area of involvement within the lower respiratory tract (i.e., vascular, bronchial, alveolar, interstitial), and narrowing the list of potential differential diagnoses. It also helps in the formulation of a diagnostic plan (see Chapter 20). Additional diagnostic tests are necessary in most animals to establish a definitive diagnosis.

#### **Complete Blood Count**

The CBC of patients with lower respiratory tract disease may show the anemia of inflammatory disease, polycythemia secondary to chronic hypoxia, or a white blood cell response characteristic of an inflammatory process of the lungs. The hematologic changes are insensitive, however, and an absence of abnormalities cannot be used as the basis for ruling out inflammatory lung diseases. For instance, only half of dogs with bacterial pneumonia have a neutrophilic leukocytosis and left shift. Abnormalities are also not specific. For instance, eosinophilia is commonly encountered as a result of hypersensitivity or parasitic disease involving organs other than the lung.

# PULMONARY SPECIMENS AND SPECIFIC DISEASE TESTING

Based on results of the history, physical examination, thoracic radiographs, and CBC, a prioritized list of differential diagnoses is developed. Additional diagnostic tests (Fig. 19-2) are nearly always required to achieve a definitive diagnosis, which is necessary for optimal therapy and outcome. Selection of appropriate tests is based on the most likely differential diagnoses, the localization of disease within the lower respiratory tract (e.g., diffuse bronchial disease, single mass lesion), the degree of respiratory compromise of the patient, and the client's motivation for optimal care.

Invasive and noninvasive tests are available. Noninvasive tests have the obvious advantage of being nearly risk free but are usually aimed at confirming a specific diagnosis. Most patients with lower respiratory tract disease require collec-

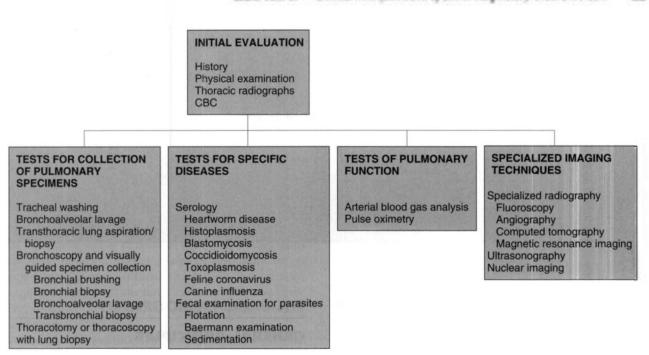


FIG 19-2
Diagnostic approach for dogs and cats with lower respiratory tract disease.

tion of a pulmonary specimen for microscopic and microbiologic analysis to further narrow the list of differential diagnoses or make a definitive diagnosis. Although the procedures for specimen collection from the lung are considered invasive, they carry varying degrees of risk, depending on the procedure used and the degree of respiratory compromise of the patient. The risk is minimal in many instances.

Noninvasive tests include serology for pulmonary pathogens, fecal examinations for parasites, and specialized imaging techniques such as fluoroscopy, angiography, computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and nuclear imaging. Techniques for collection of pulmonary specimens that can be performed without specialized equipment include tracheal wash, bronchoalveolar lavage, and transthoracic lung aspiration. Visually guided specimens can be collected during bronchoscopy. Bronchoscopy has the additional benefit of allowing visual assessment of the airways. If analysis of lung specimens and results of reasonable noninvasive tests

do not provide a diagnosis in a patient with progressive disease, thoracoscopy or thoracotomy with lung biopsy is indicated.

Valuable information about patients with lower respiratory tract disease can also be obtained by assessing lung function through arterial blood gas analysis. Results are rarely helpful in making a final diagnosis, but they are useful in determining degree of compromise and in monitoring response to therapy. Pulse oximetry, a noninvasive technique to measure oxygen saturation of the blood, is particularly valuable in monitoring patients with respiratory compromise during anesthetic procedures or respiratory crises.

#### Suggested Readings

Hamlin RL: Physical examination of the pulmonary system, Vet Clin N Am Small Anim Pract 30:1175, 2000.

Kotlikoff MI et al: Lung sounds in veterinary medicine. Part II: Deriving clinical information from lung sounds, *Compend Cont Ed Pract Vet* 6:462, 1984.

# CHAPTER Diagnostic Tests for the Lower Respiratory Tract

#### CHAPTER OUTLINE

THORACIC RADIOGRAPHY

General Principles

Trachea

Lungs

**ANGIOGRAPHY** 

**ULTRASONOGRAPHY** 

COMPUTED TOMOGRAPHY AND MAGNETIC

**RESONANCE IMAGING** 

NUCLEAR IMAGING

**PARASITOLOGY** 

SEROLOGY

TRACHEAL WASH

**Techniques** 

Specimen Handling

Interpretation of Results

#### NONBRONCHOSCOPIC BRONCHOALVEOLAR

LAVAGE

Technique for NB-BAL in Cats

Technique for NB-BAL in Dogs

Recovery of Patients Following BAL

Specimen Handling

Interpretation of Results

Diagnostic Yield

TRANSTHORACIC LUNG ASPIRATION AND

**BIOPSY** 

Techniques

**BRONCHOSCOPY** 

Technique

THORACOTOMY OR THORACOSCOPY WITH LUNG

**BIOPSY** 

**BLOOD GAS ANALYSIS** 

Techniques

Interpretation of Results

PULSE OXIMETRY

Methodology

Interpretation

#### THORACIC RADIOGRAPHY

#### **GENERAL PRINCIPLES**

Thoracic radiographs play an integral role in the diagnostic evaluation of dogs and cats with clinical signs related to the lower respiratory tract. They are also indicated for the evaluation of animals with vague, nonspecific signs of disease to detect occult pulmonary disease. Thoracic radiographs can be helpful in localizing disease processes, narrowing and prioritizing the differential diagnoses, determining the extent of disease involvement, and monitoring the progression of disease and response to treatment.

A minimum of two views of the thorax should be taken in all dogs and cats. Right lateral and ventrodorsal (VD) views usually are preferred. The sensitivity of radiographs in the detection of lesions is improved if both right and left lateral views are obtained. These are indicated if disease of the right middle lung lobe, metastatic disease, or other subtle changes are suspected. The side of the lung away from the table is more aerated, thereby providing more contrast for soft-tissue opacities, and is slightly magnified compared with the side against the table. Dorsoventral (DV) views are taken to evaluate the dorsal pulmonary arteries in animals with suspected heartworm disease, pulmonary thromboembolism, or pulmonary hypertension. The combination of DV and VD views has the same advantages as the combination of right and left lateral views in detecting subtle changes in the dorsally oriented vessels. DV, rather than VD, views are taken to minimize stress in animals in respiratory distress. Horizontal-beam lateral radiographs with the animal standing can be used to evaluate animals with suspected cavitary lesions or pleural effusion.

Careful technique is essential to ensure that thoracic radiographs are obtained that yield useful information. Poor technique can lead to either underinterpretation or overinterpretation of abnormalities. Appropriate film, settings, and development procedures should be used, and the films should be interpreted using proper lighting. The settings used are recorded so that the same technique can be used when obtaining future films, which allows for more critical

comparison of the progression of disease. The dog or cat should be restrained adequately to prevent movement, and a short exposure time is used.

Radiographs should be taken during maximum inspiration. Fully expanded lungs provide the most air contrast for soft-tissue opacities, and motion is also minimized during this phase of the respiratory cycle. Radiographic indications of maximum inspiration include widening of the angle between the diaphragm and vertebral column (representing maximal expansion of caudal lung lobes); a lucent region in front of the heart shadow (representing maximal expansion of the cranial lung lobes); flattening of the diaphragm; minimal contact between the heart and the diaphragm; and a well-delineated, nearly horizontal vena cava. Radiographs of the lungs obtained during phases of respiration other than peak inspiration are difficult to interpret. For example, incomplete expansion of the lungs can cause increased pulmonary opacities to be seen that appear pathologic, resulting in misdiagnosis.

Animals that are panting should be allowed to calm down before thoracic radiographs are obtained. A paper bag can be placed over the animal's muzzle to increase the concentration of carbon dioxide in the inspired air, causing the animal to take deeper breaths. It may be necessary to sedate some animals.

All structures of the thorax should be evaluated systematically in every animal to enhance diagnostic accuracy. Extrapulmonary abnormalities may develop secondary to pulmonary disease and may be the only radiographic finding (e.g., subcutaneous emphysema after tracheal laceration). Conversely, pulmonary disease may occur secondary to other evident thoracic diseases, such as mitral valve insufficiency, megaesophagus, and neoplasia of the body wall.

#### TRACHEA

The trachea and, in young animals, the thymus are recognizable in the cranial mediastinum. Radiographs of the cervical trachea must also be taken in dogs and cats with suspected upper airway obstruction or primary tracheal disease, most notably tracheal collapse. During evaluation of the trachea, it is important to obtain radiographs of the cervical portion during inspiration and of the thorax during both inspiration and expiration.

Only the inner wall of the trachea should be visible. If the outer wall of the trachea is identified, this is suggestive of pneumomediastinum. The trachea normally has a uniform diameter and is straight, deviating ventrally from the vertebral bodies on lateral views as it progresses toward the carina. It may appear elevated near the carina if the heart is enlarged or pleural effusion is present. Flexion or extension of the neck may cause bowing of the trachea. On VD views the trachea may deviate to the right of midline in some dogs. The tracheal cartilage becomes calcified in some older dogs and chondrodystrophic breeds.

The overall size and continuity of the tracheal lumen should also be evaluated. The normal tracheal lumen is nearly as wide as the laryngeal lumen. Hypoplastic tracheas



FIG 20-1 Lateral radiograph of a Bulldog with a hypoplastic trachea. The tracheal lumen (narrow arrows) is less than half the size of the larynx (broad arrows).

have a lumen less than half the normal size (Fig. 20-1). Strictures and fractured cartilage rings can cause an abrupt, localized narrowing of the air stripe. Mass lesions in the tissues adjacent to the trachea can compress the trachea, causing a more gradual, localized narrowing of the air stripe. In animals with extrathoracic tracheal collapse, the tracheal air stripe is narrowed in the cervical region during inspiration. In animals with intrathoracic tracheal collapse, the air stripe is narrowed on thoracic films during expiration. Fluoroscopy, available primarily through referral centers, provides a more sensitive assessment of tracheal collapse. Finally, the air contrast of the trachea sometimes allows foreign bodies or masses to be visualized within the trachea. Most foreign bodies lodge at the level of the carina or within the bronchi. The inability to radiographically identify a foreign body does not rule out the diagnosis, however.

#### LUNGS

The clinician must be careful not to overinterpret lung abnormalities on thoracic radiographs. A definitive diagnosis is not possible in most animals, and microscopic examination of pulmonary specimens, further evaluation of the heart, or testing for specific diseases is necessary. The lungs are examined for the possible presence of four major abnormal patterns: vascular, bronchial, alveolar, and interstitial. Mass lesions are considered with the interstitial patterns. Lung lobe consolidation, atelectasis, pulmonary cysts, and lung lobe torsions are other potential abnormalities. Animals with severe respiratory distress but normal thoracic radiograph findings usually have thromboembolic disease or have suffered a very recent insult to the lungs, such as trauma or aspiration (Box 20-1).

#### Vascular Pattern

The pulmonary vasculature is assessed by evaluating the vessels to the cranial lung lobes on the lateral view and the



Common Lower Respiratory Tract Differential Diagnoses for Dogs and Cats with Respiratory Signs and Normal Thoracic Radiographs

#### **Respiratory Distress**

Pulmonary thromboembolism Acute aspiration Acute pulmonary hemorrhage Acute foreign body inhalation

#### Cough

Canine infectious tracheobronchitis Canine chronic bronchitis Collapsing trachea Feline bronchitis (idiopathic) Acute foreign body inhalation Gastroesophageal reflux\*

\* Gastroesophageal reflux is a common cause of cough in people. Documentation in dogs and cats is limited, but the possibility should also be considered.

vessels to the caudal lung lobes on the VD or DV view. Normally, the blood vessels should taper gradually from the left atrium (pulmonary vein) or right ventricle (pulmonary arteries) toward the periphery of the lungs. Companion arteries and veins should be similar in size. Arteries and veins have a consistent relationship with each other and the associated bronchus. On lateral radiographs the pulmonary artery is dorsal and the pulmonary vein is ventral to the bronchus. On VD or DV radiographs the pulmonary artery is lateral and the pulmonary vein is medial to the bronchus. Vessels that are pointed directly toward or away from the X-ray beam are "end-on" and appear as circular nodules. They are distinguished from lesions by their association with a linear vessel and adjacent bronchus.

Abnormal vascular patterns generally involve an increase or decrease in the size of arteries or veins (Box 20-2). The finding of arteries larger than their companion veins indicates the presence of pulmonary hypertension or thromboembolism, most commonly caused by heartworm disease, a finding seen in both dogs and cats (Fig. 20-2). The pulmonary arteries often appear tortuous and truncated in such animals. Concurrent enlargement of the main pulmonary artery and right side of the heart may be seen in affected dogs. There may also be interstitial, bronchial, or alveolar infiltrates in cats and dogs with heartworm disease as a result of concurrent inflammation, edema, or hemorrhage.

Veins larger than their companion arteries indicate the presence of congestion resulting from left-sided heart failure. Pulmonary edema may also be present.

Dilation of both arteries and veins is an unusual finding, except in young animals. The finding of pulmonary over-circulation is suggestive of left-to-right cardiac or vascular shunts, such as patent ductus arteriosus and ventricular septal defects.



Differential Diagnoses for Dogs and Cats with Abnormal Pulmonary Vascular Patterns on Thoracic Radiographs

#### **Enlarged Arteries**

Heartworm disease Pulmonary thromboembolism Pulmonary hypertension

#### **Enlarged Veins**

Left-sided heart failure

#### **Enlarged Arteries and Veins (Pulmonary Overcirculation)**

Left-to-right shunts

Patent ductus arteriosus Ventricular septal defect Atrial septal defect

#### **Small Arteries and Veins**

Pulmonary undercirculation Cardiovascular shock Hypovolemia

- Severe dehydration
- Blood loss
- Hypoadrenocorticism

Pulmonic valve stenosis

Hyperinflation of the lungs Feline bronchitis (idiopathic)

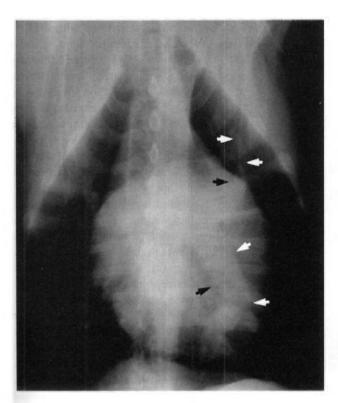
Allergic bronchitis

The finding of smaller-than-normal arteries and veins may indicate the presence of pulmonary undercirculation or hyperinflation. Undercirculation most often occurs in combination with microcardia resulting from hypoadreno-corticism or other causes of severe hypovolemia. Pulmonic stenosis may also cause radiographically visible undercirculation in some dogs. Hyperinflation is associated with obstructive airway disease, such as allergic or idiopathic feline bronchitis.

#### **Bronchial Pattern**

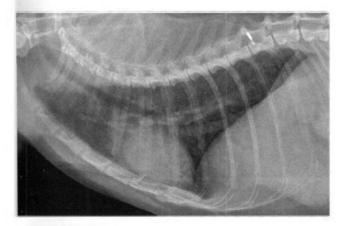
Bronchial walls are normally most easily discernible radiographically at the hilus. They should taper and grow thinner as they extend toward the periphery of each lung lobe. Bronchial structures are not normally visible radiographically in the peripheral regions of the lungs. The cartilage may be calcified in older dogs and chondrodystrophic breeds, making the walls more prominent but still sharply defined.

A bronchial pattern is caused by thickening of the bronchial walls or bronchial dilation. Thickened bronchial walls are visible as "tram lines" and "doughnuts" in the peripheral regions of the lung (Fig. 20-3). Tram lines are produced by airways that run transverse to the X-ray beam, causing the appearance of parallel thick lines with an air stripe in between. Doughnuts are produced by airways that are pointing directly toward or away from the beam, causing a thick



#### FIG 20-2

Dilation of pulmonary arteries is apparent on this ventrodorsal view of the thorax in a dog with heartworm disease. The artery to the left caudal lung lobe is extremely enlarged. *Arrowheads* delineate the borders of the arteries to the left cranial and caudal lobes.



#### FIG 20-3

A bronchointerstitial pattern is present in this lateral radiograph from a cat with idiopathic bronchitis. The bronchial component results from thickening of the bronchial walls and is characterized by "doughnuts" and "tram lines." In this radiograph the bronchial changes are most apparent in the caudal lung lobes.

circle to be seen radiographically, with the airway lumen creating the "hole." The walls of the bronchi tend to be indistinct. The finding of thickened walls indicates the presence of bronchitis and results from an accumulation of mucus or exudate along the walls within the lumens, an infiltration of



Differential Diagnoses for Dogs and Cats with Bronchial Patterns on Thoracic Radiographs\*

Canine chronic bronchitis
Feline bronchitis (idiopathic)
Allergic bronchitis
Canine infectious tracheobronchitis
Bacterial infection
Mycoplasmal infection
Pulmonary parasites

\* Bronchial disease can occur in conjunction with parenchymal lung disease. See Boxes 20-4 to 20-6 for more differential diagnoses if mixed patterns are present.

inflammatory cells within the walls, muscular hypertrophy, epithelial hyperplasia, or a combination of these changes. Potential causes of bronchial disease are listed in Box 20-3.

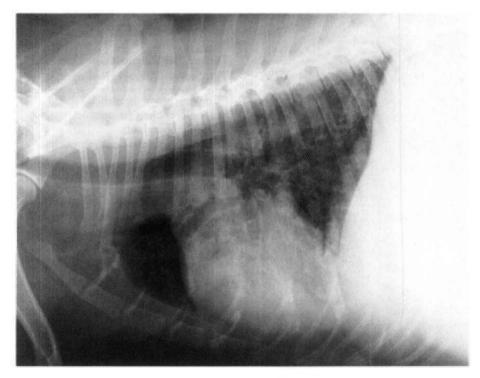
Chronic bronchial disease can result in irreversible dilation of the airways, which is termed *bronchiectasis*. It is identified radiographically by the presence of widened, nontapering airways (Fig. 20-4). Bronchiectasis can be cylindrical (tubular) or saccular (cystic). Cylindrical bronchiectasis is characterized by fairly uniform dilation of the airway. Saccular bronchiectasis additionally has localized dilations peripherally that can lead to a honeycomb appearance. All major bronchi are usually affected.

#### **Alveolar Pattern**

Alveoli are not normally visible radiographically. Alveolar patterns occur when the alveoli are filled with fluid-dense material (Box 20-4). The fluid opacity may be caused by edema, inflammation, hemorrhage, or neoplastic infiltrates, which generally originate from the interstitial tissues. The fluid-filled alveoli are silhouetted against the walls of the airways they surround. The result is a visible stripe of air from the airway lumen in the absence of definable airway walls. This stripe is an air bronchogram (Fig. 20-5). If the fluid continues to accumulate, the airway lumen will eventually also become filled with fluid, resulting in the formation of solid areas of fluid opacity, or consolidation.

Edema most often results from left-sided heart failure (see Chapter 22). In dogs the fluid initially accumulates in the perihilar region, and eventually the entire lung is affected. In cats patchy areas of edema can be present initially throughout the lung fields. The finding of enlarged pulmonary veins supports the cardiac origin of the infiltrates. Noncardiogenic edema is typically most severe in the caudal lung lobes.

Inflammatory infiltrates can be caused by infectious agents, noninfectious inflammatory disease, or neoplasia. The location of the infiltrative process can often help establish a tentative diagnosis. For example, diseases of airway origin, such as most bacterial and aspiration pneumonias, primarily affect the dependent lung lobes (i.e., the right middle and cranial lobes and the left cranial lobe). In con-



**FIG 20-4**Lateral radiograph of a dog with chronic bronchitis and bronchiectasis. The airway lumens are greatly enlarged, and normal tapering of the airway walls is not seen.

## BOX 20-4

Differential Diagnoses for Dogs and Cats with Alveolar Patterns on Thoracic Radiographs\*

#### **Pulmonary Edema**

#### Severe Inflammatory Disease

Bacterial pneumonia Aspiration pneumonia

#### Hemorrhage

Pulmonary contusion Pulmonary thromboembolism Neoplasia Fungal pneumonia Systemic coagulopathy

\* Any of the differential diagnoses for interstitial patterns (Boxes 20-5 and 20-6) can cause an alveolar pattern if associated with severe inflammation, edema, or hemorrhage.

trast, diseases of vascular origin, such as dirofilariasis and thromboemboli, primarily affect the caudal lung lobes. Localized processes involving only one lung lobe suggest the presence of a foreign body, neoplasia, abscess, granuloma, or lung lobe torsion.

Hemorrhage usually results from trauma. Thromboembolism, neoplasia, coagulopathies, and fungal infections can also cause hemorrhage into the alveoli.



FIG 20-5

Lateral view of the thorax of a dog with aspiration pneumonia. An alveolar pattern is evident by the increased soft-tissue opacity with air bronchograms. Air bronchograms are bronchial air stripes without visible bronchial walls. In this radiograph the pattern is most severe in the ventral (dependent) regions of the lung, consistent with bacterial or aspiration pneumonia.

#### **Interstitial Pattern**

The pulmonary interstitial tissues confer a fine, lacy pattern to the pulmonary parenchyma of many dogs and cats as they age, in the absence of clinically apparent respiratory disease. They are not normally visible on inspiratory radiographs in young adult animals.

Abnormal interstitial patterns are reticular (unstructured), nodular, or reticulonodular in appearance. A nodular interstitial pattern is characterized by the finding of roughly circular, fluid-dense lesions in one or more lung lobes. However, the nodules must be nearly 1 cm in diameter to be routinely detected. Interstitial nodules may represent active or inactive inflammatory lesions or neoplasia (Box 20-5).

Active inflammatory nodules often have poorly defined borders. Mycotic infections typically result in the formation of multiple, diffuse nodules. The nodules may be small (miliary; Fig. 20-6) or large and coalescing. Parasitic granulomas are often multiple, although paragonimiasis can result in the formation of a single pulmonary nodule. Abscesses can form as a result of foreign bodies or as a sequela to bacterial pneumonia. Nodular patterns may also be seen on the radiographs obtained in animals with some eosinophilic lung diseases and idiopathic interstitial pneumonias.

Inflammatory nodules can persist as inactive lesions after the disease resolves. In contrast to active inflammatory nodules, however, the borders of inactive nodules are often well demarcated. Nodules may also become mineralized in some conditions, such as histoplasmosis. Well-defined, small, inactive nodules are sometimes seen in healthy older dogs without a history of disease. Radiographs taken several months later in these animals typically show no change in the size of these inactive lesions.

Neoplastic nodules may be singular or multiple (Fig. 20-7). They are often well defined, although secondary inflammation, edema, or hemorrhage can obscure the margins. There is no radiographic pattern that is diagnostic for neoplasia. Lesions caused by parasites, fungal infections,

BOX 20-5

Differential Diagnoses for Dogs and Cats with Nodular Interstitial Patterns

#### Neoplasia

#### **Mycotic Infection**

Blastomycosis Histoplasmosis Coccidioidomycosis

#### **Pulmonary Parasites**

Aelurostrongylus infection Paragonimus infection

#### Abscess

Bacterial pneumonia Foreign body

**Eosinophilic Lung Disease** 

Idiopathic Interstitial Pneumonias

**Inactive Lesions** 

and some eosinophilic lung diseases or idiopathic interstitial pneumonias may be indistinguishable from neoplastic lesions. In the absence of strong clinical evidence, malignant neoplasia must be confirmed cytologically or histologically. If this is not possible, radiographs can be obtained again 4 weeks later to evaluate for progression of disease.

Neoplastic involvement of the pulmonary parenchyma cannot be totally excluded on the basis of thoracic radiograph findings because malignant cells are present for a while before lesions reach a radiographically detectable size. The sensitivity of radiography in identifying neoplastic nodules can be improved by obtaining left and right lateral views of the thorax.

The reticular interstitial pattern is characterized by a diffuse, unstructured, lacy increase in the opacity of the pulmonary interstitium, which partially obscures normal



FIG 20-6

Lateral view of the thorax in a dog with blastomycosis. A miliary, nodular interstitial pattern is present. Increased soft-tissue opacity above the base of heart may be the result of hilar lymphadenopathy.

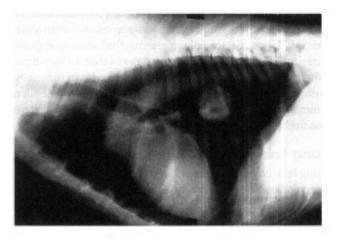


FIG 20-7

Lateral view of the thorax of a dog with malignant neoplasia. A well-circumscribed, solid, circular mass is present in the caudal lung field. Papillary adenocarcinoma was diagnosed after surgical excision.

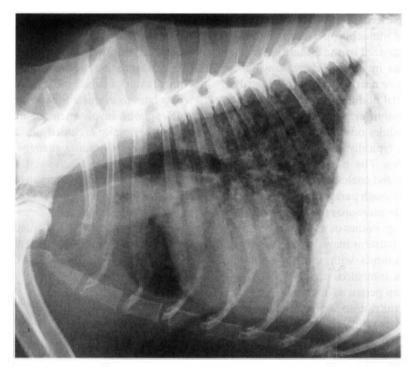


FIG 20-8
Lateral radiograph of a dog with pulmonary carcinoma. An unstructured pattern is present as well as an increased bronchial pattern.

vascular and airway markings. Reticular interstitial patterns frequently occur in conjunction with nodular interstitial patterns (also called *reticulonodular patterns*) and alveolar and bronchial patterns (Fig. 20-8).

The increased reticular interstitial opacity can result from edema, hemorrhage, inflammatory cells, neoplastic cells, or fibrosis within the interstitium (Box 20-6). The interstitial space surrounds the airways and vessels and is normally extremely small in dogs and cats. With the continued accumulation of fluid or cells, however, the alveoli can become flooded, which produces an alveolar pattern. Visible focal interstitial accumulations of cells, or nodules, can also develop with time. Any of the diseases associated with alveolar and interstitial nodular patterns can cause a reticular interstitial pattern early in the course of disease (see Boxes 20-4 and 20-5). This pattern is also often seen in older dogs with no clinically apparent disease, presumably as a result of pulmonary fibrosis; this further decreases the specificity of the finding.

#### **Lung Lobe Consolidation**

Lung lobe consolidation is characterized by a lung lobe that is entirely soft-tissue opacity (Fig. 20-9, A). Consolidation occurs when an alveolar or interstitial disease process progresses to the point at which the entire lobe is filled with fluid or cells. Common differential diagnoses for lung lobe consolidation are severe bacterial or aspiration pneumonia (essentially resulting in an abscess of the entire lobe), neoplasia, lung lobe torsion, and hemorrhage. The inhalation of



Differential Diagnoses for Dogs and Cats with Reticular (Unstructured) Interstitial Patterns

#### Pulmonary Edema (Mild)

#### Infection

Viral pneumonia Bacterial pneumonia Toxoplasmosis Mycotic pneumonia Parasitic infection (more often bronchial or nodular interstitial pattern)

#### Neoplasia

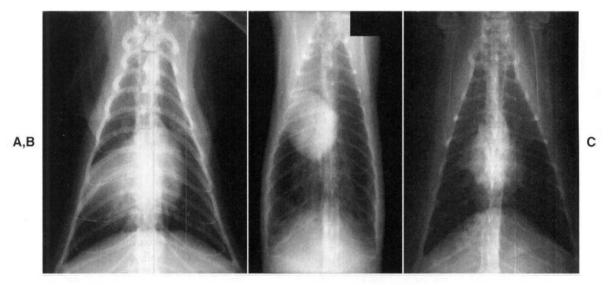
#### **Eosinophilic Lung Disease**

#### **Idiopathic Interstitial Pneumonias**

Idiopathic pulmonary fibrosis

#### Hemorrhage (Mild)

plant material can also result in consolidation of the involved lung lobe as a result of the inflammatory reaction to the foreign material and secondary infection. This differential diagnosis should be considered especially in regions of the country where foxtails are prevalent.



Thoracic radiographs from three different patients, ventrodorsal projections. Radiograph A shows consolidation of the right middle lung lobe caused by neoplasia. Note that the soft tissue density of the lung silhouettes with the shadow of the heart. Radiograph B shows atelectasis of the middle region of the right lung and marked hyperinflation of the remaining lungs in a cat with idiopathic bronchitis. Note the shift of the heart shadow toward the collapsed region. Radiograph C shows atelectasis of the right middle lung lobe in another cat with idiopathic bronchitis. In this patient the adjacent lung lobes have expanded into the area previously occupied by the right middle lobe, preventing displacement of the

#### **Atelectasis**

Atelectasis is also characterized by a lobe that is entirely softtissue opacity. In this instance the lobe is collapsed as a result of airway obstruction. All the air within the lobe has been absorbed and not replaced. It is distinguished from consolidation by the small size of the lobe (Fig. 20-9, *B*). Often the heart is displaced toward the atelectatic lobe. Atelectasis is most commonly seen involving the right middle lobe of cats with bronchitis (Fig. 20-9, *C*). Displacement of the heart may not occur in these cats.

#### **Cavitary Lesions**

Cavity lesions describe any abnormal air accumulation in the lung. They can be congenital, acquired, or idiopathic. Specific types of cavitary lesions include bullae, which result from ruptured alveoli due to congenital weakness of tissues and/or small airway obstruction, such as in some cats with idiopathic bronchitis; blebs, which are bullae located within the pleura; and cysts, which are cavitary lesions lined by airway epithelium. Parasitic "cysts" (not lined by epithelium) can form around *Paragonimus* worms. Thoracic trauma is a common cause of cavitary lesions. Other differential diagnoses include neoplasia, lung infarction (from thromboembolism), abscess, and granuloma. Cavitary lesions may be apparent as localized accumulations of air or

fluid, often with a partially visible wall (Fig. 20-10). An airfluid interface may be visible using standing horizontal-beam projections. Bullae and blebs are rarely apparent radiographically.

Cavitary lesions may be discovered incidentally or on thoracic radiographs of dogs and cats with spontaneous pneumothorax. If pneumothorax is present, surgical excision of the lesion is usually indicated (see Chapter 25). If inflammatory or neoplastic disease is suspected, further diagnostic testing is indicated. If the lesion is found incidentally, animals can be periodically reevaluated radiographically to determine whether the lesion is progressing or resolving. If the lesion does not resolve during the course of 1 to 3 months, surgical removal is considered for diagnostic purposes and to prevent potentially life-threatening spontaneous pneumothorax.

#### **Lung Lobe Torsion**

Lung lobe torsion can develop spontaneously in deep-chested dogs or as a complication of pleural effusion or pneumonectomy in dogs and cats. The right middle and left cranial lobes are most commonly involved. The lobe usually twists at the hilus, obstructing the flow of blood into and out of the lung lobe. Venous drainage is obstructed before arterial flow, causing the lung lobe to become congested with blood. Over



**FIG 20-10**Ventrodorsal view of the thorax in a cat showing a cystic lesion (arrowheads) in the left caudal lung lobe. Differential diagnoses included neoplasia and *Paragonimus* infection.

time, air is absorbed from the alveoli and atelectasis can occur.

Lung lobe torsion is difficult to identify radiographically. Severe bacterial or aspiration pneumonia resulting in consolidation of these same lobes is far more common and produces similar radiographic changes. The finding of pulmonary vessels or bronchi traveling in an abnormal direction is strongly suggestive of torsion. Unfortunately, pleural fluid, if not present initially, often develops and obscures the radiographic image of the affected lobe. Ultrasonography is often useful in detecting a torsed lung lobe. Bronchoscopy, bronchography, computed tomography, or thoracotomy is necessary to confirm the diagnosis in some animals.

#### ANGIOGRAPHY

Angiography can be used to confirm a diagnosis of pulmonary thromboembolism. Obstructed arteries are blunted or do not show the normal gentle taper and arborization.

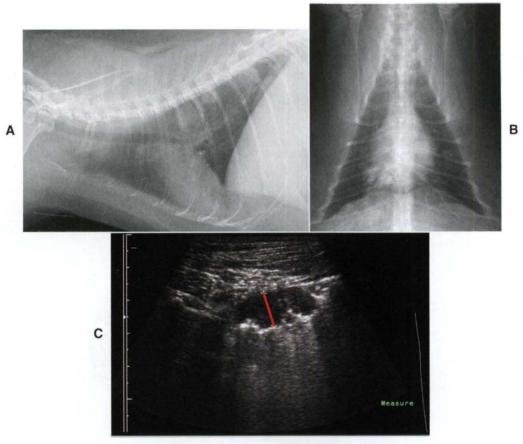
Arteries may appear dilated and tortuous. There also may be localized areas of extravasated contrast agent. If several days have elapsed since the embolization occurred, however, lesions may no longer be identifiable; therefore angiography should be performed as soon as the disorder is suspected and the animal's condition is stabilized. Angiography may also be used as a confirmatory test in cats with presumptive dirofilariasis but negative adult antigen blood test results and echocardiographic findings (see Chapter 10).

#### **ULTRASONOGRAPHY**

Ultrasonography is used to evaluate pulmonary mass lesions adjacent to the body wall, diaphragm, or heart and also consolidated lung lobes (Fig. 20-11). Because air interferes with the sound waves, aerated lungs and structures surrounded by aerated lungs cannot be examined. However, some patients with a reticular interstitial pattern on thoracic radiographs have sufficient infiltrates to be visualized where they abut the body wall. The consistency of lesions often can be determined to be solid, cystic, or fluid filled. Some solid masses are hypolucent and appear to be cystic on ultrasonograms. Vascular structures may be visible, particularly with Doppler ultrasound, and this can be helpful in identifying lung lobe torsion. Ultrasonography can also be used to guide needles or biopsy instruments into solid masses for specimen collection. It is used for evaluating the heart in animals with clinical signs that cannot be readily localized to either the cardiac or the respiratory systems. Ultrasonographic evaluation of patients with pleural disorders is discussed in Chapter 24.

# COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Computed tomography (CT) and magnetic resonance imaging (MRI) are used routinely in human medicine for the diagnostic evaluation of lung disease. The accessibility of CT in particular has led to its increased use in dogs and cats. The resultant three-dimensional images are more sensitive and specific for the identification of certain airway, vascular, and parenchymal diseases as compared with thoracic radiography. In a study of dogs with metastatic neoplasia, only 9% of nodules detected by CT were identified by thoracic radiography (Nemanic et al., 2006). Examples of cases that may benefit from CT include those with possible metastatic disease; possible pulmonary thromboembolism; idiopathic interstitial pneumonias, including idiopathic pulmonary fibrosis; or potentially excisable disease (to determine the extent and location of disease and the potential involvement of other structures, such as the major vessels). The application of CT and MRI to the diagnosis of specific canine and feline pulmonary diseases requires further investigation.



#### FIG 20-11

Multiple pulmonary nodules are easily visible on the lateral radiograph (A) from a cat with a one year history of cough and recent episodes of respiratory distress with wheezing. Nodules do not obviously extend to the chest wall based on the ventrodorsal radiograph (B). However, a 1-cm mass was found on ultrasonagraphic examination of the right thorax (C; a red line has been positioned between the ultrasound markers to indicate site of measurement). An ultrasound-guided aspirate was performed. The presence of eosinophils in the aspirate prompted the performance of fecal examinations for pulmonary parasites, and a diagnosis of paragonimiasis was made through the identification of characteristic ova.

#### **NUCLEAR IMAGING**

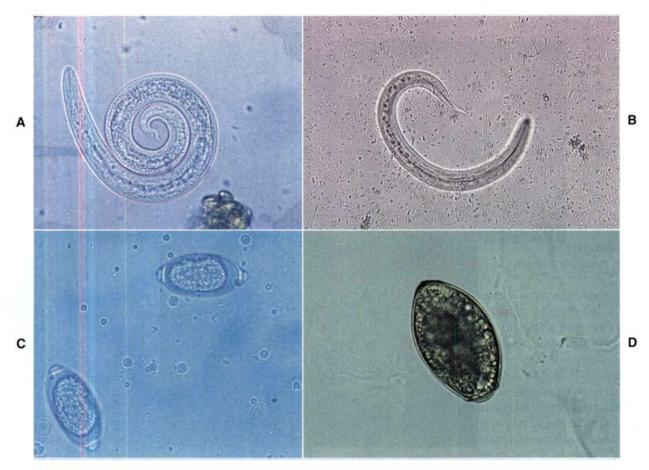
Mucociliary clearance can be measured by placing a drop of technetium-labeled albumin at the carina and observing its movement with a gamma camera to assist in the diagnosis of ciliary dyskinesia. Nuclear imaging can be used for the relatively noninvasive measurement of pulmonary perfusion and ventilation, valuable for the diagnosis of pulmonary thromboembolism. Restrictions for handling radioisotopes and the need for specialized recording equipment limit the availability of these tools to specialty centers.

#### **PARASITOLOGY**

Parasites involving the lower respiratory tract are identified by direct observation, blood tests, cytologic analysis of respiratory tract specimens, or fecal examinations. Oslerus osleri reside in nodules near the carina, which can be identified bronchoscopically. Rarely, other parasites may be seen. Blood tests are often used to diagnose heartworm disease (see Chapter 10).

Larvae that may be present in fluid from tracheal or bronchial washings include *O. osleri, Aelurostrongylus abstrusus* (Fig. 20-12, *A*), and *Crenosoma vulpis* (Fig. 20-12, *B*). Eggs that may be present include those of *Capillaria (Eucoleus) aerophila* and *Paragonimus kellicotti* (Fig. 20-12, *C* and *D*). Larvated eggs or larvae from *Filaroides hirthi* or *Aelurostrongylus milksi* can be present but are rarely associated with clinical signs. The more common organisms are described in Table 20-1.

The hosts of lung parasites generally cough up and swallow the eggs or larvae, which are then passed in the feces to infect the next host or an intermediate host. Fecal exami-



**FIG 20-12 A,** Larva of Aelurostrongylus abstrusus. **B,** Larva of Crenosoma vulpis. **C,** Double operculated ova of Capillaria sp. **D,** Single operculated ova of Paragonimus kellicotti.

nation for eggs or larvae is a simple, noninvasive tool for the diagnosis of such infestations. However, because shedding is intermittent, parasitic disease cannot be included solely on the basis of negative fecal examination findings. Multiple (at least three) examinations should be performed in animals that are highly suspected of having parasitic disease. If possible, several days should be allowed to elapse between each collection of feces.

Routine fecal flotation can be used to concentrate eggs from *C. aerophila*. High-density fecal flotation (specific gravity [s.g.], 1.30 to 1.35) can be used to concentrate *P. kellicotti* eggs. Sedimentation techniques are preferred for concentrating and identifying *P. kellicotti* eggs, particularly if few eggs are present. Larvae are identified through the use of the Baermann technique. However, *O. osleri* larvae are insufficiently motile for reliable identification with this technique, and zinc sulfate (s.g., 1.18) flotation is recommended. Even so, false-negative results are common in cases with *O. osleri*. All of these techniques can be readily performed at minimal expense. Methods for sedimentation and the Baermann technique are described in Boxes 20-7 and 20-8.

Toxoplasma gondii occasionally causes pneumonia in dogs and cats. Dogs do not shed Toxoplasma organisms in the feces, but cats may. However, the shedding of eggs is part of the direct life cycle of the organisms and does not correlate with the presence of systemic disease resulting from the indirect cycle. Infection is therefore diagnosed by finding tachyzoites in pulmonary specimens or indirectly on the basis of serologic findings.

Migrating intestinal parasites can cause transient pulmonary signs in young animals. Migration most often occurs before the mature adults develop in the intestine, and thus eggs may not be found in feces.

## **SEROLOGY**

Serologic tests can detect a variety of pulmonary pathogens. Antibody tests provide only indirect evidence of infection, however. In general, they should be used only to confirm a suspected diagnosis, not to screen for disease. Whenever possible, identification of the infectious organisms is the preferred method of diagnosis. Tests available for common



## TABLE 20-1

## Characteristics of Eggs or Larvae from Respiratory Parasites

PARASITE	HOST	STAGE	SOURCE	DESCRIPTION
Capillaria aerophila	Dog and cat	Eggs	Routine flotation of feces, airway specimens	Barrel shaped, yellow, with prominent, transparent, asymmetric bipolar plugs; slightly smaller than <i>Trichuris</i> eggs; 60-80 µm × 30-40 µm
Paragonimus kellicotti	Dog and cat	Eggs	High-density flotation or sedimentation of feces, airway specimens	Oval, golden-brown, single, operculated; operculum flat with prominent shoulders; 75-118 μm × 42-67 μm
Aelurostrongylus abstrusus	Cat	Larvae	Baermann technique of feces, airway specimens	Larvae with S-shaped tail; dorsal spine present; 350-400 μm × 17 μm; eggs or larvated eggs may be seen in airway specimens
Oslerus osleri	Dog	Larvae, eggs	Tracheal wash, bronchial brushing of nodules, zinc sulfate flotation of feces	Larvae have S-shaped tail without dorsal spine; rarely found eggs are thin-walled, colorless, and larvated; 80 × 50 μm
Crenosoma vulpis	Dog	Larvae	Baermann technique of feces, airway specimens	Larvae have tapered tail without severe kinks or spines; 250-300 μm; larvated eggs may be seen in airway specimens



## BOX 20-7

#### Sedimentation of Feces for Concentration of Eggs

- Homogenize 1 to 3 g of feces with water (at least 30 ml).
- Pass through coarse sieve or gauze (250-µm mesh), washing debris remaining in sieve with fine spray of water.
- 3. Pour filtrate into conical urine flask, and let stand for 2 minutes.
- 4. Discard most of supernate.
- 5. Pour remaining 12 to 15 ml into flat-bottomed tube, and let stand for 2 minutes.
- 6. Draw off supernate.
- 7. Add 2 to 3 drops of 5% methylene blue.
- 8. Examine under low power.

Data from Urquhart GM et al: *Veterinary parasitology,* ed 2, Oxford, 1996, Blackwell Science.

pulmonary pathogens include those for *Histoplasma*, *Blastomyces*, *Coccidiodomyces*, *Toxoplasma*, and feline coronavirus. These tests are discussed fully in Chapter 92. Antibody tests for canine influenza are discussed further in Chapter 22. Serum antigen tests for *Cryptococcus* (see Chapter 98) and adult heartworms are also available (see Chapter 10). Antibody tests for dirofilariasis are available and used primarily to support the diagnosis of feline heartworm disease (see Chapter 10).



## BOX 20-8

#### Baermann Technique for Concentration of Larvae

- 1. Set up apparatus.
  - a. Glass funnel supported in ring stand
  - b. Rubber tube attached to bottom of funnel, and closed with a clamp
  - c. Coarse sieve (250-µm mesh) placed in top of funnel
  - d. Double-layer gauze on top of sieve
- 2. Place feces on gauze in funnel.
- 3. Fill funnel slowly with water to immerse feces.
- 4. Leave overnight at room temperature.
- Collect water via rubber tube from neck of funnel in a Petri dish.
- 6. Examine under low power.

Data from Urquhart GM et al: *Veterinary parasitology,* ed 2, Oxford, 1996, Blackwell Science.

## TRACHEAL WASH

## **Indications and Complications**

Tracheal wash can yield valuable diagnostic information in animals with cough or respiratory distress resulting from disease of the airways or pulmonary parenchyma and in animals with vague presenting signs and pulmonary abnormalities detected on thoracic radiographs (i.e., most animals with lower respiratory tract disease). Tracheal wash is generally performed after results of the history, physical examination, thoracic radiography, and other routine components of the database are known.

Tracheal wash provides fluid and cells that can be used to identify discases involving the major airways while bypassing the normal flora and debris of the oral cavity and pharynx. The fluid obtained is evaluated cytologically and microbiologically and therefore should be collected before the initiation of antibiotic treatment whenever possible. Tracheal wash is likely to provide a representative specimen in patients with bronchial or alveolar disease (Table 20-2). It is less likely to identify interstitial and small focal disease processes. However, the procedure is inexpensive and minimally invasive, and this makes it reasonable to perform in most animals with lower respiratory tract disease if the risks of other methods of specimen collection are deemed too great. Potential complications are rare, and they include tracheal laceration, subcutaneous emphysema, and pneumomediastinum. Bronchospasm may be induced by the procedure in patients with hyperreactive airways, particularly cats with bronchitis.

## **TECHNIQUES**

Tracheal wash is performed using transtracheal or endotracheal techniques. Transtracheal wash is performed by passing a catheter into the trachea to the level of the carina through the cricothyroid ligament or between the tracheal rings in an awake or sedated animal. Endotracheal wash is performed by passing a catheter through an endotracheal tube in an anesthetized animal. The endotracheal technique is preferred in cats and very small dogs, although either technique can be used in any animal. Patients with airways that may be hyperreactive, particularly cats, are treated with bronchodilators (see the section on endotracheal technique).

## Transtracheal Technique

Transtracheal wash fluid is collected using an 18- to 22gauge through-the-needle intravenous catheter (e.g., Intracath; Becton, Dickinson and Company). The catheter should be long enough to reach the carina, which is located at approximately the level of the fourth intercostal space. The longest intravenous catheter available may be 12 inches (30 cm), which is long enough to reach from the cricothyroid ligament to the carina in most dogs. However, it may be necessary to insert the catheter between tracheal rings in giant-breed dogs to ensure that it reaches the carina. Alternatively, a 14-gauge, short, over-the-needle catheter is used to enter the trachea at the cricothyroid ligament and a 3.5F polypropylene male dog urinary catheter is passed through the catheter into the airways. The ability of the urinary catheter to pass through the 14-gauge catheter should be tested each time before the procedure is performed.

The dog can sit or lie down, depending on what position is more comfortable for the animal and clinician. The dog is restrained with its nose pointing toward the ceiling at about 45 degrees from horizontal (Fig. 20-13, A). Overextension of the neck causes the animal to be more resistant. Dogs that cannot be restrained should be tranquilized. If tranquilization is needed, premedication with atropine or glycopyrrolate is recommended to minimize contamination of the trachea with oral secretions. Narcotics are avoided to preserve the cough reflex, which can facilitate the retrieval of fluid.

The cricothyroid ligament is identified by palpating the trachea in the ventral cervical region and following it dorsally toward the larynx to the raised, smooth, narrow band of the cricoid cartilage. Immediately above the cricoid cartilage is a depression, where the cricothyroid ligament is located (Fig. 20-13, B). If the trachea is entered above the cricothyroid ligament, the catheter is passed dorsally into the pharynx and a nondiagnostic specimen is obtained. Such dorsal passage of the catheter often results in excessive gagging and retching.

Lidocaine is always injected subcutaneously at the site of entry. The skin over the cricothyroid ligament is prepared surgically, and sterile gloves are worn to pass the catheter. The needle of the catheter is held with the bevel facing ventrally. The skin over the ligament is then tented, and the needle is passed through the skin. The larynx is stabilized with the nondominant hand. To properly stabilize it, the clinician should grasp at least 180 degrees of the circumference of the airway between the fingers and thumb. Failure to hold the airway firmly is the most common technical mistake made. Next, the tip of the needle is rested against the cricothyroid ligament and inserted through the ligament with a quick, short motion.

The hand stabilizing the trachea is then used to pinch the needle at the skin, with the hand kept firmly in contact with the neck, while the catheter is threaded into the trachea with the other hand. By keeping the hand holding the needle against the neck of the animal so that the hand, needle, and neck can move as one, the clinician prevents laceration of the larynx or trachea and inadvertent removal of the needle from the trachea. Threading the catheter provokes coughing. There should be little or no resistance to the passage of the catheter. Elevating the hub of the needle slightly so that the tip points more ventrally or retracting the needle a few millimeters facilitates passage of the catheter if it is lodged against the opposite tracheal wall. The catheter itself should not be pulled back through the needle because the tip can be sheared off within the airway by the cutting edge of the needle.

Once the catheter is completely threaded into the airway, the needle is withdrawn and the catheter guard is attached to prevent shearing of the catheter. The person restraining the animal now holds the catheter guard against the neck of the animal so that movement of the neck will not dislodge the catheter. The head can be restrained in a natural position.

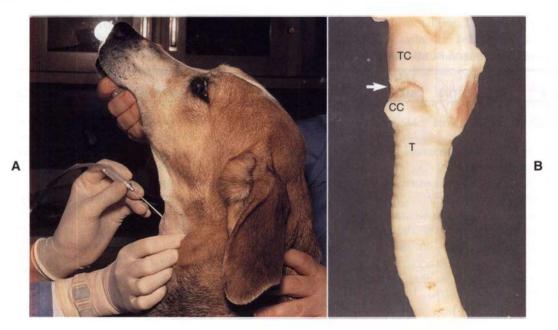
It is convenient to have four to six 12-ml syringes ready, each filled with 3 to 5 ml of 0.9% sterile preservative-free sodium chloride solution. The entire bolus of saline in one



TABLE 20-2

Comparisons of Techniques for Collecting Specimens from the Lower Respiratory Tract

TECHNIQUE	SITE OF COLLECTION	SPECIMEN SIZE	ADVANTAGES	DISADVANTAGES	INDICATIONS
Tracheal wash	Large airways	Moderate	Simple technique Minimal expense No special equipment Complications rare Volume adequate for cytology and culture	Airway must be involved for specimen to represent disease May induce bronchaspasm in patients with hyperreactive airways, particularly cats	Bronchial and alveolar disease Because of safety and ease, consider for any lung disease Less likely to be representative of interstitial or small focal processes
Bronchoalveolar lavage	Small airways, alveoli, sometimes interstitium	Large	Simple technique Nonbronchoscopic technique requires no special equipment and minimal expense Bronchoscopic technique allows airway evaluation and directed sampling Resultant hypoxemia is transient and responsive to oxygen supplementation Safe for animals in stable condition Large volume of lung sampled High cytologic quality large volume for analysis	General anesthesia required Special equipment and expertise required for bronchoscopic collection Generally not recommended for animals with increased respiratory efforts or respiratory distress Capability to provide oxygen supplementation is required May induce bronchospasm in patients with hyperreactive airways, particularly cats	Small airway, alveolar, or interstitial disease Routine during bronchoscopy
Lung aspirate	Interstitium, alveoli when flooded	Small	Simple technique Minimal expense No special equipment Solid masses adjacent to body wall: excellent representation with minimal risk	Potential for complications:    pneumothorax,    hemothorax,    pulmonary hemorrhage Relatively small area of    lung sampled Specimen adequate only    for cytology Specimen blood    contaminated	Solid masses adjacent to chest wall (for solitary/ localized disease, see also Thoracotomy or Thoracoscopy with Lung Biopsy) Diffuse interstitial disease
Thoracotomy or thoracoscopy with lung biopsy	Small airways, alveoli, interstitium	Large	Ideal specimen Allows histologic examination in addition to culture	Relatively expensive Requires expertise Requires general anesthesia Major surgical procedure	Localized process where excision may be therapeutic as well as diagnostic Any progressive disease not diagnosed by less invasive methods



#### FIG 20-13

**A,** To perform a transtracheal wash, the animal is restrained in a comfortable position with the nose pointed toward the ceiling. The ventral neck is clipped and scrubbed, and the clinician wears sterile gloves. The cricothyroid ligament is identified as described in **B.** After an injection of lidocaine, the needle of the catheter is placed through the skin. The larynx is grasped firmly with the fingers and thumb at least 180 degrees around the airway. The needle can then be inserted through the cricothyroid ligament into the airway lumen. **B,** The lateral view of this anatomic specimen demonstrates the trachea and larynx in a position similar to that of the dog in **A.** The cricothyroid ligament (arrow) is identified by palpating the trachea (T) from ventral to dorsal until the raised cricoid cartilage (CC) is palpated. The cricothyroid ligament is the first depression above the cricoid cartilage. The cricothyroid ligament attaches cranially to the thyroid cartilage (TC). The palpable depression above the thyroid cartilage (not shown) should not be entered.

syringe is injected into the catheter. Immediately after this, many aspiration attempts are made. After each aspiration, the syringe must be disconnected from the catheter and the air evacuated without losing any of the retrieved fluid. Aspirations should be forceful and repeated at least five or six times so that small volumes of airway secretions that have been aspirated into the catheter are pulled the entire length of the catheter into the syringe.

The procedure is repeated using additional boluses of saline until a sufficient amount of fluid is retrieved for analysis. A total of 1.5 to 3 ml of turbid fluid is adequate in most instances. The clinician does not need to be concerned about "drowning" the animal with the infusion of the modest volumes of fluid described because the fluid is rapidly absorbed into the circulation. Failure to retrieve adequate volumes of visibly turbid fluid can be the result of several technical difficulties, as outlined in Figure 20-14.

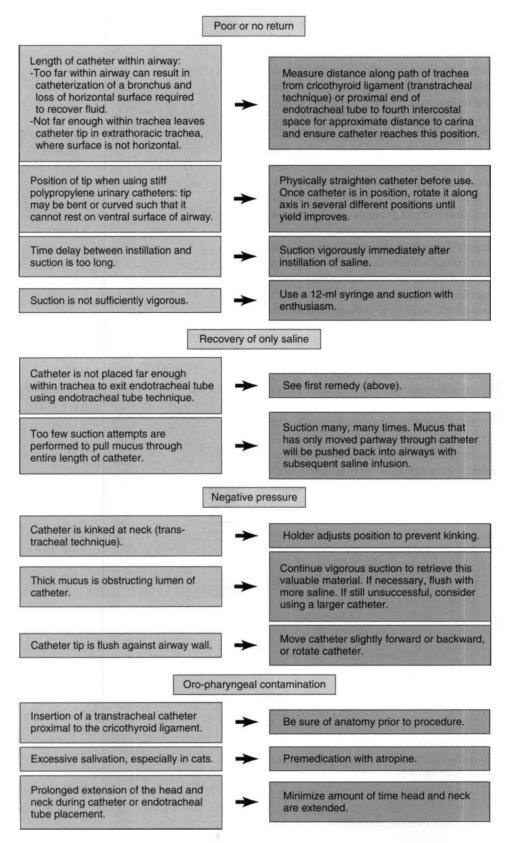
The catheter is removed after sufficient fluid is collected. A sterile gauze sponge with antiseptic ointment is then immediately placed over the catheter site, and a light bandage is wrapped around the neck. This bandage is left in place for several hours while the animal rests quietly in a cage. These precautions minimize the likelihood that subcutaneous emphysema or pneumomediastinum will develop.

### **Endotracheal Technique**

The endotracheal technique is performed by passing a 3.5-5F male dog urinary catheter through a sterilized endotracheal tube. The animal is anesthetized with a short-acting intravenous agent to a sufficient depth to allow intubation. A short-acting barbiturate, propofol, or, in cats, a combination of ketamine and acepromazine or diazepam is effective. Premedication with atropine, particularly in cats, is recommended to minimize contamination of the trachea with saliva. Cats with lower respiratory tract disease may have airway hyperreactivity and generally should be administered a bronchodilator before the tracheal wash. Terbutaline (0.01 mg/kg) can be given subcutaneously to cats not already receiving oral bronchodilators. It is also prudent to keep a metered dose inhaler of albuterol at hand to administer through the endotracheal tube or by mask if breathing becomes labored.

A sterilized endotracheal tube should be passed without dragging the tip through the oral cavity. The animal's mouth is opened wide with the tongue pulled out, a laryngoscope is used, and, in cats, sterile topical lidocaine is applied to the laryngeal cartilages to ease passage of the tube with minimal contamination.

The urinary catheter is passed through the endotracheal tube to the level of the carina (approximately the fourth



#### FIG 20-14

Overcoming problems with tracheal wash fluid collection. Green boxes indicate problems, blue boxes indicate possible causes, and orange boxes indicate remedies.

intercostal space), maintaining sterile technique. The wash procedure is performed as described for the transtracheal technique. Slightly larger boluses of saline may be required, however, because of the larger volume of the catheter. Use of a catheter larger than 5F seems to reduce the yield of the wash except when secretions are extremely viscous.

#### SPECIMEN HANDLING

The cells collected in the wash fluid are fragile. The fluid is ideally processed within 30 minutes of collection, with minimal manipulation. Bacterial culture is performed on at least 0.5 to 1 ml of fluid. Fungal cultures are performed if mycotic disease is a differential diagnosis, and Mycoplasma cultures are considered for cats and dogs with signs of bronchitis. Cytologic preparations are made both from the fluid and from any mucus within the fluid. Both fluid and mucus are examined because infectious agents and inflammatory cells can be concentrated in the mucus, but the proteinaceous material causes cells to clump and interferes with evaluation of the cell morphology. Mucus is retrieved with a needle, and squash preparations are made. Direct smears of the fluid itself can be made, but such specimens are often hypocellular. Sediment or cytocentrifuge preparations are generally necessary to make adequate interpretation possible. Straining the fluid through gauze to remove the mucus is discouraged because infectious agents may be lost in the process. Routine cytologic stains are used.

Microscopic examination of slides includes the identification of cell types, qualitative evaluation of the cells, and an examination for infectious agents. Cells are evaluated qualitatively for evidence of macrophage activation, neutrophil degeneration, lymphocyte reactivity, and characteristics of malignancy. Epithelial hyperplasia secondary to inflammation should not be overinterpreted as neoplasia, however. Infectious agents such as bacteria, protozoa (*Toxoplasma gondii*), fungi (*Histoplasma, Blastomyces*, and *Cryptococcus* organisms), and parasitic larvae or eggs may be present (see Fig. 20-12, and Figs. 20-15 through 20-17). Because only one or two organisms may be present on an entire slide, a thorough evaluation is indicated.

### INTERPRETATION OF RESULTS

Normal tracheal wash fluid contains primarily respiratory epithelial cells. Few other inflammatory cells are present (Fig. 20-18). Occasionally, macrophages are retrieved from the small airways and alveoli because the catheter was extended into the lungs beyond the carina or because relatively large volumes of saline were used. Most macrophages are not activated. In these instances the presence of macrophages does not indicate disease but rather reflects the acquisition of material from the deep lung (see the section on nonbronchoscopic bronchoalveolar lavage).

Slides are examined for evidence of overt oral contamination, which can occur during transtracheal washing if the catheter needle was inadvertently inserted proximal to the cricothyroid ligament. Rarely, dogs can cough the catheter up into the oropharynx. Oral contamination can also result

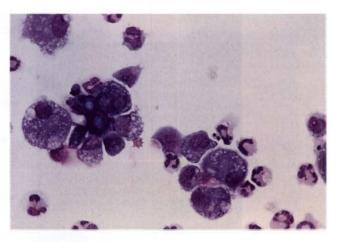


FIG 20-15

Photomicrograph of a *Blastomyces* organism from the lungs of a dog with blastomycosis. The organisms stain deeply basophilic, are 5 to 15  $\mu m$  in diameter, and have a thick refractile cell wall. Often, as in this figure, broad-based budding forms are seen. The cells present are alveolar macrophages and neutrophils. (Bronchoalveolar lavage fluid, Wright stain.)

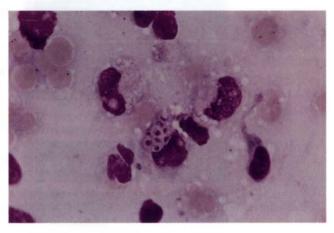
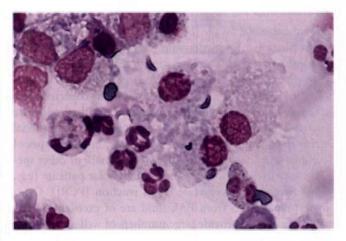


FIG 20-16

Photomicrograph of *Histoplasma* organisms from the lungs of a dog with histoplasmosis. The organisms are small (2 to 4 pm) and round, with a deeply staining center and a lighter-staining halo. They are often found within phagocytic cells: in this figure, an alveolar macrophage. (Bronchoalveolar lavage fluid, Wright stain.)

from drainage of saliva into the trachea, which usually occurs in cats that hypersalivate or dogs that are heavily sedated, particularly if the head and neck are extended more than briefly for the passage of the endotracheal tube or transtracheal catheter. Oral contamination is indicated by the finding of numerous squamous epithelial cells, often coated with bacteria, and *Simonsiella* organisms (Fig. 20-19). *Simonsiella* organisms are large basophilic rods that are frequently found stacked uniformly on one another along their broad side. Specimens with overt oral contamination generally do not provide accurate information about the airways, particularly with regard to bacterial infection.

Cytologic results of tracheal wash fluid are most useful when pathogenic organisms or malignant cells are identified. The presence of pathogens such as Toxoplasma gondii, systemic fungal organisms, and parasites provide a definitive diagnosis. The finding of bacterial organisms in cytologic preparations without evidence of oral contamination indicates the presence of infection. The growth of any of the systemic mycotic agents in culture is also clinically signifi-

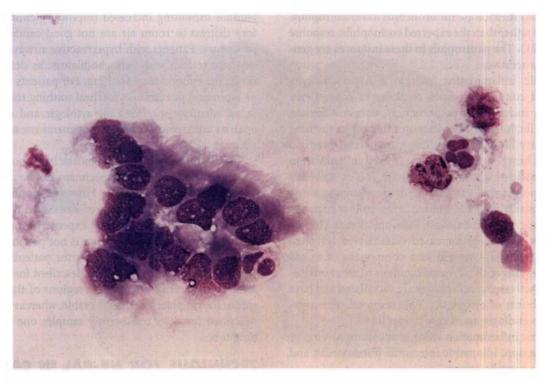


Photomicrograph of Toxoplasma gondii tachyzoites from the lungs of a cat with acute toxoplasmosis. The extracellular tachyzoites are crescent shaped with a centrally placed nucleus. They are approximately 6 µm in length. (Bronchoalveolar lavage fluid, Wright stain.)

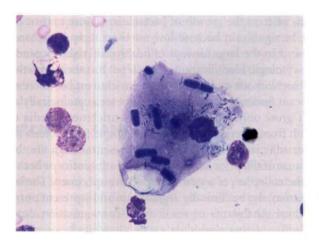
cant, whereas the growth of bacteria in culture may or may not be significant because low numbers of bacteria can be present in the large airways of healthy animals. In general, the cytologic identification of bacteria and their growth in culture without multiplication in enrichment broth are significant findings. Bacteria that are not seen cytologically and that grow only after incubation in enrichment media can result from several situations. For example, the bacteria may be causing infection without being present in high numbers because of the prior administration of antibiotics or because of the collection of a nonrepresentative specimen. The bacteria may also be clinically insignificant and represent normal tracheal inhabitants or result from contamination during collection. Other clinical data must therefore be considered when interpreting such findings. The role of *Mycoplasma* sp. in respiratory disease of the dog and cat is not well understood. These organisms cannot be seen on cytologic preparations and are difficult to grow in culture. Specific transport media is necessary. Growth of Mycoplasma organisms from tracheal wash fluid may indicate primary or secondary infection or be an insignificant finding. Treatment is generally recommended.

Criteria of malignancy for making a diagnosis of neoplasia must be interpreted with extreme caution. Overt characteristics of malignancy must be present in many cells in the absence of concurrent inflammation for a definitive diagnosis to be made.

The type of inflammatory cells present in tracheal wash fluid can assist in narrowing the differential diagnoses, although a mixed inflammatory response is common.



Tracheal wash fluid from a healthy dog showing ciliated epithelium and few inflammatory cells.



#### FIG 20-19

Tracheal wash fluid showing evidence of oropharyngeal contamination. The numerous, uniformly stacked basophilic rods are *Simonsiella* organisms, normal inhabitants of the oral cavity. These organisms, as well as many other bacteria, are adhering to a squamous epithelial cell. Squamous epithelium is another indication of contamination from the oral cavity.

Neutrophilic (suppurative) inflammation is common in bacterial infections. Before antibiotic therapy is initiated, the neutrophils may be (but are not always) degenerative, and organisms can often be seen. Neutrophilic inflammation may be a response to a variety of other diseases. For instance, it can be caused by other infectious agents or seen in patients with canine chronic bronchitis, idiopathic pulmonary fibrosis or other idiopathic interstitial pneumonias, or even neoplasia. Some cats with idiopathic bronchitis have neutrophilic inflammation rather than the expected eosinophilic response (see Chapter 21). The neutrophils in these instances are generally nondegenerative.

Eosinophilic inflammation reflects a hypersensitivity response, and common diseases resulting in eosinophilic inflammation include allergic bronchitis, parasitic disease, and eosinophilic lung disease. Parasites that affect the lung include primary lungworms or flukes, migrating intestinal parasites, and heartworms. Over time, mixed inflammation can occur in patients with hypersensitivity. It is occasionally possible for nonparasitic infections or neoplasia to cause eosinophilia, usually as part of a mixed inflammatory response.

Macrophagic (granulomatous) inflammation is characterized by the finding of increased numbers of activated macrophages, generally present as a component of mixed inflammation along with increased numbers of other inflammatory cells. Activated macrophages are vacuolated and have increased amounts of cytoplasm. This response is nonspecific unless an etiologic agent can be identified.

Lymphocytic inflammation alone is uncommon. Viral or rickettsial infection, idiopathic interstitial pneumonias, and lymphoma are considerations.

True hemorrhage can be differentiated from a traumatic specimen collection by the presence of erythrophagocytosis and hemosiderin-laden macrophages. An inflammatory response is also usually present. Hemorrhage can be caused by neoplasia, mycotic infection, heartworm disease, thromboembolism, foreign body, lung lobe torsion, or coagulopathies. Evidence of hemorrhage is seen occasionally in animals with congestive heart failure or severe bacterial pneumonia.

## NONBRONCHOSCOPIC BRONCHOALVEOLAR LAVAGE

## **Indications and Complications**

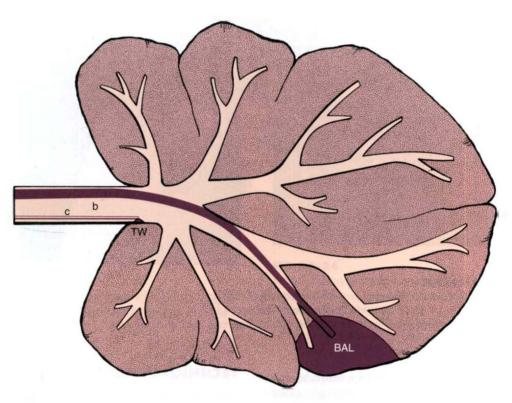
Bronchoalvelolar lavage (BAL) is considered for the diagnostic evaluation of patients with lung disease involving the small airways, alveoli, or interstitium that are not in respiratory distress (see Table 20-2). A large volume of lung is sampled by BAL (Figs. 20-20 and 20-21). The collected specimens are of large volume, providing more than adequate material for routine cytology, cytology involving special stains (e.g., Gram stains, acid-fast stains), multiple types of cultures (e.g., bacterial, fungal, mycoplasmal), or other specific tests that might be helpful in particular patients (e.g., flow cytometry, polymerase chain reaction [PCR]). Cytologic preparations from BAL fluid are of excellent quality and consistently provide large numbers of well-stained cells for examination.

Although general anesthesia is required, the procedure is associated with few complications and can be performed repeatedly in the same animal to follow the progression of disease or observe the response to therapy. The primary complication of BAL is transient hypoxemia. The hypoxemia generally can be corrected with oxygen supplementation, but animals exhibiting increased respiratory efforts or respiratory distress in room air are not good candidates for this procedure. Patients with hyperreactive airways, particularly cats, are treated with bronchodilators, as described previously, for endotracheal washing. For patients with bacterial or aspiration pneumonia, tracheal washing routinely results in an adequate specimen for cytologic and microbiologic analysis and avoids the need for general anesthesia in these patients.

BAL is a routine part of diagnostic bronchoscopy, during which visually guided BAL specimens can be collected from specific diseased lung lobes. However, nonbronchoscopic techniques (NB-BAL) have been developed that allow BAL to be performed with minimal expense in routine practice settings. Because visual guidance is not possible using these methods, they are used primarily for patients with diffuse disease. However, the technique described for cats probably samples the cranial and middle regions of the lung on the side of the cat placed against the table, whereas the technique described for dogs consistently samples one of the caudal lung lobes.

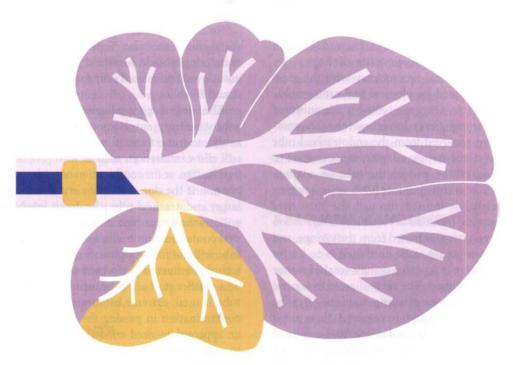
### **TECHNIQUE FOR NB-BAL IN CATS**

A sterile endotracheal tube and syringe adapter are used in cats to collect lavage fluid (Fig. 20-22; see also Fig. 20-21). Cats, particularly those with signs of bronchitis, should be



#### FIG 20-20

The region of the lower respiratory tract that is sampled by bronchoalveolar lavage (BAL) in comparison with the region sampled by tracheal wash (TW). The solid red line (b) within the airways represents a bronchoscope or modified feeding tube. The open lines (c) represent the tracheal wash catheter. Bronchoalveolar lavage yields fluid representative of the deep lung, whereas tracheal wash yields fluid representative of processes involving major airways.



#### FIG 20-21

The region of the lower respiratory tract presumed to be sampled by nonbronchoscopic bronchoalveolar lavage in cats using an endotracheal tube.



**FIG 20-22**Bronchoalveolar lavage using an endotracheal tube in a cat. The fluid retrieved is grossly foamy because of the surfactant present. The procedure is performed quickly because the airway is completely occluded during the infusion and aspiration of fluid.

treated with bronchodilators before the procedure, as described previously for tracheal wash (endotracheal technique), to decrease the risk of bronchospasm. The cat is premedicated with atropine (0.05 mg/kg subcutaneously) and anesthetized with ketamine and acepromazine or diazepam, given intravenously. The endotracheal tube is passed as cleanly as possible through the larynx to minimize oral contamination. To achieve sufficient cleanliness, the tip of the tongue is pulled out, a laryngoscope is used, and sterile lidocaine is applied topically to the laryngeal mucosa. The cuff is then inflated sufficiently to create a seal, but overinflation is avoided to prevent tracheal rupture (i.e., use a 3-ml syringe and inflate cuff in 0.5-ml increments only until no leak is audible when gentle pressure is placed on the oxygen reservoir bag).

The cat is placed in lateral recumbency with the most diseased side, as determined by physical and radiographic findings, against the table. Oxygen (100%) is administered for several minutes through the endotracheal tube. The anesthetic adapter is then removed from the endotracheal tube and replaced with a sterile syringe adapter, using caution to avoid contamination of the end of the tube or adapter. Immediately, a bolus of warmed, sterile 0.9% saline solution (5 ml/kg body weight) is infused through the tube over approximately 3 seconds. Immediately after infusion, suction is applied by syringe. Air is eliminated from the syringe, and several aspiration attempts are made until fluid is no longer recovered. The procedure is repeated using a total of two or three boluses of saline solution. The cat is allowed to expand its lungs between the infusions of saline solution. After the last infusion, the syringe adapter is removed (because it greatly interferes with ventilation) and excess fluid is drained from the large airways and endotracheal tube by elevating the caudal half of the cat a few inches off of the table. At this point, the cat is cared for as described in the section on recovery of patients after BAL.

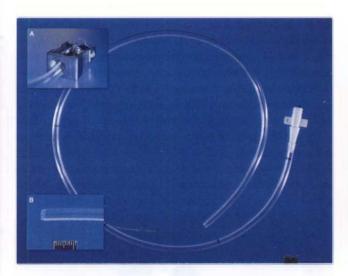
## TECHNIQUE FOR NB-BAL IN DOGS

An inexpensive 122-cm 16F Levin-type polyvinyl chloride stomach tube (Argyle stomach tube, Tyco Healthcare Group LP) can be used in dogs to collect lavage fluid. The tube must be modified for successful NB-BAL. Sterile technique is maintained throughout. The distal end of the tube is cut off to remove the side openings. The proximal end is cut off to remove the flange and shorten the tube to a length slightly greater than the distance from the open end of the dog's endotracheal tube to the last rib. A syringe adapter is placed within the proximal end of the tube (Fig. 20-23).

Recovery of BAL fluid can be improved by tapering the distal end of the tube. Tapering is readily achieved using a metal, single-blade, handheld pencil sharpener that has been autoclaved and is used only for this purpose (see Fig. 20-23, *A* and *B*).

The dog is premedicated with atropine (0.05 mg/kg subcutaneously) or glycopyrrolate (0.005 mg/kg subcutaneously) and anesthetized using a short-acting protocol that will allow intubation, such as with propofol, a short-acting barbiturate, or the combination of medetomidine and butorphanol. If the dog is of sufficient size to accept a size 6 or larger endotracheal tube, the dog is intubated with a sterile endotracheal tube placed as cleanly as possible to minimize oral contamination of the specimen. The modified stomach tube will not fit through a smaller endotracheal tube, so the technique must be performed without an endotracheal tube or a smaller stomach tube must be used. If no endotracheal tube is used, extreme care must be taken to minimize oral contamination in passing the modified stomach tube, and an appropriate-sized endotracheal tube should be available to gain control of the airway in case of complications and for recovery.

Oxygen (100%) is provided through the endotracheal tube or by face mask for several minutes. The modified



#### FIG 20-23

The catheter used for nonbronchoscopic bronchoalveolar lavage in dogs is a modified 16F Levin-type stomach tube. The tube is shortened by cutting off both ends. A simple pencil sharpener (inset A) is used to taper the distal end of the tube (inset B). A syringe adapter is added to the proximal end. Sterility is maintained throughout.

stomach tube is passed through the endotracheal tube using sterile technique until resistance is felt. The goal is to wedge the tube snugly into an airway rather than have it abut an airway division. Therefore the tube is withdrawn slightly, then passed again, until resistance is consistently felt at the same depth. Rotating the tube slightly during passage may help achieve a snug fit. Remember that if the endotracheal tube is not much larger than the stomach tube, ventilation is restricted at this point and the procedure should be completed expediently.

For medium-size dogs and larger, two 35-ml syringes are prepared in advance, each with 25 ml of saline and 5 ml of air. While the modified stomach tube is held in place, a 25-ml bolus of saline is infused through the tube, followed by the 5 ml of air, by holding the syringe upright during infusion (Fig. 20-24). Gentle suction is applied immediately after infusion, using the same syringe. It may be necessary to withdraw the tube slightly if negative pressure is felt. The tube should not be withdrawn more than a few millimeters. If it is withdrawn too far, air will be recovered instead of fluid. The second bolus of saline is infused and recovered in the same manner, with the tube in the same position. The dog is cared for as described in the next section.

In very small dogs, it is prudent to reduce the volume of saline used in each bolus, particularly if a smaller diameter stomach tube is used. Overinflation of the lungs with excessive fluid volumes should be avoided.

## RECOVERY OF PATIENTS FOLLOWING BAL

Regardless of the method used, BAL causes a transient decrease in the arterial oxygen concentration, but this hypoxemia responds readily to oxygen supplementation. Where

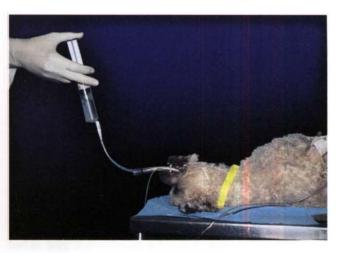


FIG 20-24

Bronchoalveolar lavage using a modified stomach tube in a dog. The tube is passed through a sterile endotracheal tube and lodged in a bronchus. A syringe preloaded with saline and air is held upright during infusion so that the saline is infused first, followed by the air.

possible, patients are monitored with pulse oximetry (p. 283) before and throughout the procedure and during recovery. After the procedure, 100% oxygen is provided through an endotracheal tube for as long as the dog or cat will allow intubation. Several gentle "sighs" are performed with the anesthesia bag to help expand any collapsed portions of lung. Bronchospasms are a reported complication of BAL in people, and increased airway resistance has been documented in cats after bronchoscopy and BAL (Kirschvink et al., 2005). Albuterol in a metered dose inhaler should be on hand to administer through the endotracheal tube or by spacer and mask if needed.

After extubation the mucous membrane color, pulses, and character of respirations are monitored closely. Crackles can be heard for several hours after BAL and are not cause for concern. Treatment with oxygen supplementation is continued by mask, oxygen cage, or nasal catheter if there are any indications of hypoxemia. Oxygen supplementation is rarely necessary for more than 10 to 15 minutes after BAL, even in animals with diseased lungs; however, the ability to provide supplementation for longer periods is a prerequisite for the performance of this procedure.

#### SPECIMEN HANDLING

Successful BAL yields fluid that is grossly foamy, a result of the surfactant from the alveoli. Approximately 50% to 80% of the total volume of saline instilled is expected to be recovered. Less will be obtained from dogs with tracheobronchomalacia (collapsing airways). The fluid is placed on ice immediately after collection and is processed as soon as possible, with minimum manipulation to decrease cell lysis. For convenience, retrieved boluses can be combined for analysis; however, fluid from the first bolus usually contains more cells from the larger airways, and fluid from later boluses is more representative of the alveoli and interstitium.

The BAL fluid is analyzed cytologically and microbiologically. Nucleated cell counts are performed on undiluted fluid using a hemocytometer. Cells are concentrated onto slides for differential cell counts and qualitative analysis using cytocentrifugation or sedimentation techniques. Excelent-quality slides result that are stained using routine cytologic procedures. Differential cell counts are performed by counting at least 200 nucleated cells. Slides are scrutinized for evidence of macrophage activation, lymphocyte reactivity, neutrophil degeneration, and criteria of malignancy. All slides are examined thoroughly for possible etiologic agents, such as fungi, protozoa, parasites, and bacteria (see Figs. 20-12 and 20-15 to 20-17). As described for tracheal wash, visible strands of mucus can be examined for etiologic agents by squash preparation.

Approximately 5 ml of fluid is used for bacterial culture. Additional fluid is submitted for fungal culture if mycotic disease is among the differential diagnoses. *Mycoplasma* cultures are considered in cats and dogs with signs of bronchitis.

#### INTERPRETATION OF RESULTS

Normal cytologic values for BAL fluid are inexact because of inconsistency in the techniques used and variability among individual animals of the same species. In general, total nucleated cell counts in normal animals are less than 400 to  $500/\mu$ l. Differential cell counts from healthy dogs and cats are listed in Table 20-3.

Interpretation of BAL fluid cytology and cultures is essentially the same as that described for tracheal wash fluid, although the specimens are more representative of the deep lung than the airways. In addition, the normal cell population of macrophages must not be misinterpreted as being indicative of macrophagic or chronic inflammation (Fig. 20-25). As for all cytologic specimens, definitive diagnoses

are made through the identification of organisms or abnormal cell populations. Fungal, protozoal, or parasitic organisms may be present in extremely low numbers in BAL specimens; therefore the entire concentrated slide preparation must be carefully scanned. Profound epithelial hyperplasia can occur in the presence of an inflammatory response and should not be confused with neoplasia.

If quantitative bacterial culture is available, growth of organisms at greater than  $1.7 \times 10^3$  colony-forming units (CFU)/ml has been reported to indicate infection (Peeters et al., 2000). In the absence of quantitative numbers, growth

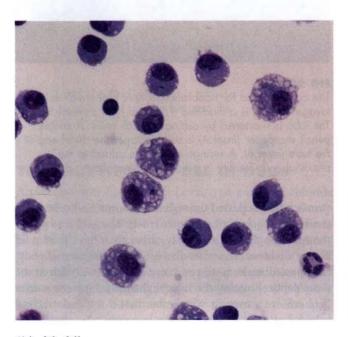


FIG 20-25
Bronchoalveolar lavage fluid from a normal dog. Note that alveolar macrophages predominate.



TABLE 20-3

Differential Cell Counts from Bronchoalveolar Lavage Fluid from Normal Animals

	BRONCHOS	COPIC BAL	NONBRONCHOSCOPIC BAL	
CELL TYPE	CANINE (%)*	FELINE (%)†	CANINE (%)‡	FELINE (%)§
Macrophages	70 ± 11	71 + 10	81 ± 11	78 ± 15
Lymphocytes	7 ± 5	5 ± 3	2 ± 5	$0.4 \pm 0.6$
Neutrophils	5 ± 5	7 ± 4	15 ± 12	5 ± 5
Eosinophils	6 ± 6	16 ± 7	2 ± 3	16 ± 14
Epithelial cells	1 ± 1	_	_	_
Mast cells	1 ± 1	<u> </u>	_	_

<sup>\*</sup> Mean ± SD, 6 clinically and histologically normal dogs. (From Kuehn NF: Canine bronchoalveolar lavage profile. Thesis for masters of science degree, West Lafayette, Ind, 1987, Purdue University.)

<sup>†</sup> Mean ± SE, 11 clinically normal cats. (From King RR et al. Bronchoalveolar lavage cell populations in dogs and cats with eosinophilic pneumonitis. In *Proceedings of the Seventh Veterinary Respiratory Symposium*, Chicago, 1988, Comparative Respiratory Society.) ‡ Mean ± SD, 9 clinically normal dogs. (From Hawkins EC et al. Use of a modified stomach tube for bronchoalveolar lavage in dogs, *J Am Vet Med Assoc* 215:1635, 1999.)

<sup>§</sup> Mean ± SD, 34 specific pathogen-free cats. (From Hawkins EC et al: Cytologic characterization of bronchoalveolar lavage fluid collected through an endotracheal tube in cats, Am J Vet Res 55:795, 1994.)

of organisms on a plate directly inoculated with BAL fluid is considered significant, whereas growth from fluid that occurs only after multiplication in enrichment broth may also be a result of normal inhabitants or contamination. Patients that are already receiving antibiotics at the time of specimen collection may have significant infection with few or no bacteria by culture.

## DIAGNOSTIC YIELD

A retrospective study of BAL fluid cytologic analysis in dogs at referral institutions showed that BAL findings provided the basis for a definitive diagnosis in 25% of cases and were supportive of the diagnosis in an additional 50%. Only dogs in which a definitive diagnosis was obtained by any means were included. Definitive diagnoses were possible on the basis of BAL only in those animals in which infectious organisms were identified or in those cases in which overtly malignant cells were present in specimens in the absence of marked inflammation. BAL has been shown to be more sensitive than radiographs in identifying pulmonary involvement with lymphosarcoma. Carcinoma was definitively identified in 57% of cases, and other sarcomas were not found in BAL fluid. Fungal pneumonia was confirmed in only 25% of cases, although organisms were found in 67% of cases in a previous study of dogs with overt fungal pneumonia.

## TRANSTHORACIC LUNG ASPIRATION AND BIOPSY

## **Indications and Complications**

Pulmonary parenchymal specimens can be obtained by transthoracic needle aspiration or biopsy. Although only a small region of lung is sampled by these methods, collection can be guided by radiographic findings or ultrasonography to improve the likelihood of obtaining representative specimens. As with tracheal wash and BAL, a definitive diagnosis will be possible in patients with infectious or neoplastic disease. Patients with non-infectious inflammatory diseases require thoracoscopy or thoracotomy with lung biopsy for a definitive diagnosis.

Potential complications of transthoracic needle aspiration or biopsy include pneumothorax, hemothorax, and pulmonary hemorrhage. The procedures are not recommended in animals with suspected cysts, abscesses, pulmonary hypertension, or coagulopathies. Severe complications are uncommon, but these procedures should not be performed unless the clinician is prepared to place a chest tube and otherwise support the animal if necessary.

Lung aspirates and biopsy specimens are indicated for the nonsurgical diagnosis of intrathoracic mass lesions that are in contact with the thoracic wall. The risk of complications in these animals is relatively low because the specimens can be collected without disrupting aerated lung. Obtaining aspirates or biopsy specimens from masses that are far from the body wall and near the mediastinum carries the additional risk of lacerating important mediastinal organs,

vessels, or nerves. If a solitary localized mass lesion is present, thoracotomy and biopsy should be considered rather than transthoracic sampling because this permits both the diagnosis of the problem and the potentially therapeutic benefits of complete excision.

Transthoracic lung aspirates can be obtained in animals with a diffuse interstitial radiographic pattern. In some of these patients, solid areas of infiltrate in lung tissue immediately adjacent to the body wall can be identified ultrasonographically even though they are not apparent on thoracic radiographs (see Fig. 20-11). Ultrasound guidance of the aspiration needle into the areas of infiltrate should improve diagnostic yield and safety. If areas of infiltrate cannot be identified ultrasonographically, BAL should be considered before lung aspiration in animals that can tolerate the procedure because it yields a larger specimen for analysis and, in this author's opinion, carries less risk than transthoracic aspiration in patients that are not experiencing increased respiratory efforts or distress. Tracheal wash (if BAL is not possible) and appropriate ancillary tests are also generally indicated before lung aspiration in these patients because they carry little risk.

#### **TECHNIQUES**

The site of collection in animals with localized disease adjacent to the body wall is best identified with ultrasonography. If ultrasonography is not available or the lesion is surrounded by aerated lung, the site is determined on the basis of two radiographic views. The location of the lesion during inspiration in all three dimensions is identified by its relationship to external landmarks: the nearest intercostal space or rib, the distance from the costochondral junctions, and the depth into the lungs from the body wall. If available, fluoroscopy or CT also can be used to guide the needle or biopsy instrument.

The site of collection in animals with diffuse disease is a caudal lung lobe. The needle is inserted between the seventh to ninth intercostal spaces, approximately two thirds of the distance from the costochondral junctions to the spine.

The animal must be restrained for the procedure, and sedation or anesthesia is necessary in some. Anesthesia is avoided, if possible, because the hemorrhage created by the procedure is not cleared as readily from the lungs in an anesthetized dog or cat. The skin at the site of collection is shaved and surgically prepared. Lidocaine is injected into the subcutaneous tissues and intercostal muscles to provide local anesthesia.

Lung aspiration can be performed with an injection needle, spinal needle, or a variety of thin-walled needles designed specifically for lung aspiration in people. Spinal needles are readily available in most practices, are sufficiently long to penetrate through the thoracic wall, and have a stylet. A 22-gauge, 1.5- to 3.5-inch (3.75- to 8.75-cm) spinal needle is usually adequate.

The clinician wears sterile gloves. The needle with stylet is advanced through the skin several rib spaces from the desired biopsy site. The needle and skin are then moved to the biopsy site. This is done because air is less likely to enter the thorax through the needle tract following the procedure if the openings in the skin and chest wall are not aligned. The needle is then advanced through the body wall to the pleura. The stylet is removed, and the needle hub is immediately covered by a finger to prevent pneumothorax until a 12-ml syringe can be placed on the hub. During inspiration the needle is thrust into the chest to a depth predetermined from the radiographs, usually about 1 inch (2.5 cm), while suction is applied to the syringe (Fig. 20-26). To keep from inserting the needle too deeply, the clinician may pinch the needle shaft with the thumb and forefinger of the nondominant hand at the desired maximum depth of insertion. During insertion the needle can be twisted along its long axis in an attempt to obtain a core of tissue. The needle is then immediately withdrawn to the level of the pleura. Several quick stabs into the lung can be made along different lines to increase the yield.

Each stab should take only a second. Prolonging the time that the needle is within the lung tissue increases the likelihood of complications. The lung tissue will be moving with respirations, resulting in laceration of tissue, even if the needle is held steady.

The needle is withdrawn from the body wall with a minimal amount of negative pressure maintained by the syringe. It is unusual for the specimen to be large enough to have entered the syringe. The needle is removed from the syringe, the syringe is filled with air and reattached to the

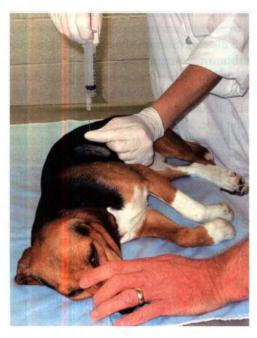


FIG 20-26

Transthoracic lung aspiration performed with a spinal needle. Note that sterile technique is used. The needle shaft can be pinched with a finger and thumb at the maximum depth to which the needle should be passed. The finger and thumb thus act as a guard to prevent overinsertion of the needle. Although this patient is under general anesthesia, this is not usually indicated.

needle, and the contents of the needle are then forced onto one or more slides. Grossly, the material is bloody in most cases. Squash preparations are made. Slides are stained using routine procedures and then evaluated cytologically. Increased numbers of inflammatory cells, infectious agents, or neoplastic cell populations are potential abnormalities. Alveolar macrophages are normal findings in parenchymal specimens and should not be interpreted as representing chronic inflammation. They should be carefully examined for evidence of phagocytosis of bacteria, fungi, or red blood cells and for signs of activation. Epithelial hyperplasia can occur in the presence of inflammation and should not be confused with neoplasia. Sometimes the liver is aspirated inadvertently, particularly in deep-chested dogs, yielding a population of cells that may resemble those from adenocarcinoma. However, hepatocytes typically contain bile pigment. Bacterial culture is indicated in some animals, although the volume of material obtained is quite small.

Transthoracic lung core biopsies can be performed in animals with mass lesions. They are collected after an aspirate has proved to be nondiagnostic. Needle biopsy instruments can be used to biopsy lesions adjacent to the chest wall (e.g., EZ Core biopsy needles, Products Group International). Smaller-bore, thin-walled lung biopsy instruments can be obtained from medical suppliers for human patients. These instruments collect smaller pieces of tissue but are less disruptive to normal lung. Ideally, sufficient material is collected for histologic evaluation. If not, squash preparations are made for cytologic studies.

#### **BRONCHOSCOPY**

## **Indications**

Bronchoscopy is indicated for the evaluation of the major airways in animals with suspected structural abnormalities, for visual assessment of airway inflammation or pulmonary hemorrhage, and as a means of collecting specimens in animals with undiagnosed lower respiratory tract disease. Bronchoscopy can be used to identify structural abnormalities of the major airways, such as tracheal collapse, mass lesions, tears, strictures, lung lobe torsions, bronchiectasis, bronchial collapse, and external airway compression. Foreign bodies or parasites may be identified. Hemorrhage or inflammation involving or extending to the large airways may also be seen and localized.

Specimen collection techniques performed in conjunction with bronchoscopy are valuable diagnostic tools because they can be used to obtain specimens from deeper regions of the lung than is possible with the tracheal wash technique, and visually directed sampling of specific lesions or lung lobes is also possible. Animals undergoing bronchoscopy must receive general anesthesia, and the presence of the scope within the airways compromises ventilation. Therefore bronchoscopy is contraindicated in animals with severe respiratory tract compromise unless the procedure is likely to be therapeutic (e.g., foreign body removal).

## **Technique**

Bronchoscopy is technically more demanding than most other endoscopic techniques. The patient is often experiencing some degree of respiratory compromise, which poses increased anesthetic and procedural risk. Airway hyperreactivity may be exacerbated by the procedure, particularly in cats.(Kirschvink et al., 2005) A small-diameter, flexible endoscope is needed and should be sterilized before use. The bronchoscopist should be thoroughly familiar with normal airway anatomy to ensure that every lobe is examined. BAL is routinely performed as part of diagnostic bronchoscopy after thorough visual examination of the airways. The reader is referred to chapters in other textbooks for details about performing bronchoscopy and bronchoscopic BAL (Kuehn, 2004; McKiernan, 2005; Hawkins, 2004). Bronchoscopic images of normal airways are shown in Fig. 20-27. Reported cell counts from bronchoscopically collected BAL fluid are provided in Table 20-3.

Abnormalities that may be observed during bronchoscopy and their common clinical correlations are listed in Table 20-4. A definitive diagnosis may not be possible on the basis of the findings yielded by gross examination alone. Specimens are collected through the biopsy channel for cytologic, histopathologic, and microbiologic analysis. Bronchial specimens are obtained by bronchial washing, bronchial brushing, or pinch biopsy. Material for bacterial culture can be collected with guarded culture swabs. The deeper lung is sampled by BAL or transbronchial biopsy. Foreign bodies are removed with retrieval forceps.

# THORACOTOMY OR THORACOSCOPY WITH LUNG BIOPSY

Thoracotomy and surgical biopsy are performed in animals with progressive clinical signs of lower respiratory tract disease that has not been diagnosed using less invasive means. Although thoracotomy carries a greater risk than the previously mentioned diagnostic techniques, the modern anesthetic agents, surgical techniques, and monitoring capabilities now available have made this procedure routine in many veterinary practices. Analgesic drugs are used to manage the postoperative pain, and complication-free animals are discharged as soon as 2 to 3 days after surgery. Surgical biopsy provides excellent-quality specimens for histopathologic analysis and culture. Abnormal lung tissue and accessible lymph nodes are biopsied.

Excisional biopsy of abnormal tissue can be therapeutic in animals with localized disease. Removal of localized neoplasms, abscesses, cysts, and foreign bodies can be curative. The removal of large localized lesions can improve the matching of ventilation and perfusion, even in animals with evidence of diffuse lung involvement, thereby improving the oxygenation of blood and reducing clinical signs.

In practices where thoracoscopy is available, this less invasive technique can be used for initial assessment of intrathoracic disease. Similarly, a "mini" thoracotomy through a

relatively small incision can be performed. If disease is obviously disseminated throughout the lungs such that surgical intervention will not be therapeutic, biopsies of abnormal tissue can be obtained with these methods via small incisions. For patients with questionable findings or apparently localized disease, thoracoscopy or "mini" thoracotomy can be transitioned to a full thoracotomy during the same anesthesia.

## **BLOOD GAS ANALYSIS**

#### **Indications**

The measurement of partial pressures of oxygen (PaO<sub>2</sub>) and carbon dioxide (PaCO<sub>2</sub>) in arterial blood specimens provides information about pulmonary function. Venous blood analysis is less useful because venous blood oxygen pressures are greatly affected by cardiac function and peripheral circulation. Arterial blood gas measurements are indicated to document pulmonary failure, to differentiate hypoventilation from other causes of hypoxemia, to help determine the need for supportive therapy, and to monitor the response to therapy. Respiratory compromise must be severe for abnormalities to be measurable because the body has tremendous compensatory mechanisms.

#### **TECHNIQUES**

Arterial blood is collected in a heparinized syringe. Dilution of specimens with liquid heparin can alter blood gas results. Therefore commercially available syringes preloaded with lyophilized heparin are recommended (e.g., Micro ABG<sup>TM</sup>, 1-ml luer slip syringe with 25-g needle and 50 U heparin, Vital Signs, Inc). Alternatively, the procedure for heparinizing syringes as described by Hopper et al. (2005) should be followed: 0.5 ml of liquid sodium heparin is drawn into a 3-ml syringe with a 25 g needle. The plunger is drawn back to the 3 ml mark. All air is then expelled from the syringe. This procedure for expelling air and excess heparin is repeated three times.

The femoral artery is commonly used (Fig. 20-28). The animal is placed in lateral recumbency. The upper rear limb is abducted, and the rear limb resting on the table is restrained in a partially extended position. The femoral artery is palpated in the inguinal region, close to the abdominal wall, using two fingers. The needle is advanced into the artery between these fingers. The artery is thick walled and loosely attached to adjacent tissues; thus the needle must be sharp and positioned exactly on top of the artery. A short, jabbing motion facilitates entry.

The dorsal pedal artery is useful for arterial collection in medium-sized and large dogs. The position of the artery is illustrated in Fig. 20-29.

Once the needle has penetrated the skin, suction is applied. On entry of the needle into the artery, blood should enter the syringe quickly, sometimes in pulses. Unless the animal is severely compromised, the blood will be bright red compared with the dark red of venous blood. Dark red blood

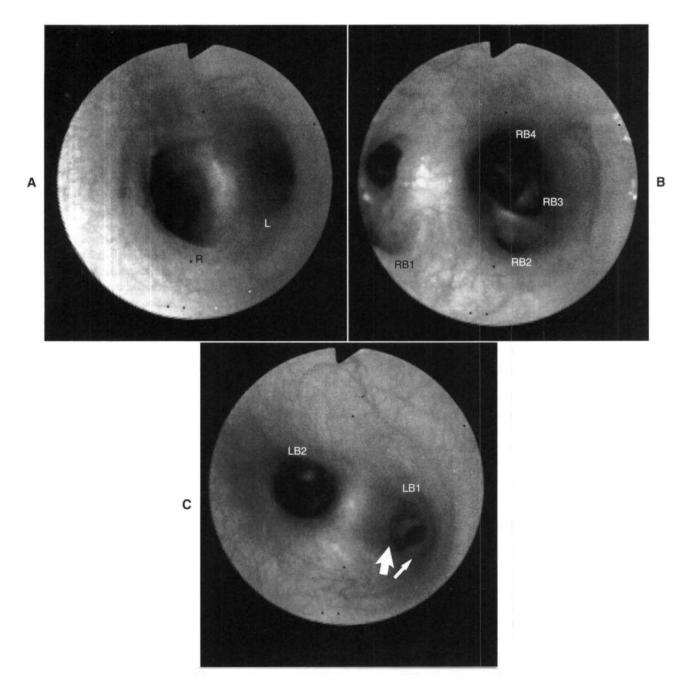


FIG 20-27

Bronchoscopic images of normal airways. The labels for the lobar bronchi are from a useful nomenclature system for the major airways and their branches by Amis et al. (1986). **A,** Carina, the division between the right (R) and left (L) mainstem bronchi. **B,** Right mainstem bronchus. The carina is off the right side of the image. The openings to the right cranial (RB1), right middle (RB2), accessory (RB3), and right caudal (RB4) bronchi are visible. **C,** Left mainstem bronchus. The carina is off the left side of the image. The openings to the left cranial (LB1) and left caudal (LB2) bronchi are visible. The left cranial lobe (LB1) divides immediately into cranial (narrow arrow) and caudal (broad arrow) branches. (Amis TC et al: Systematic identification of endobronchial anatomy during bronchoscopy in the dog, Am J Vet Res 47:2649, 1986.)

or blood that is difficult to draw into the syringe may be from a vein. Mixed samples from both the artery and vein can also be collected accidentally, particularly from the femoral site.

After removal of the needle, pressure is applied to the puncture site for 5 minutes to prevent hematoma formation.

Pressure is applied even after unsuccessful attempts if there is any possibility that the artery was entered.

All air bubbles are eliminated from the syringe. The needle is covered by a cork or rubber stopper, and the entire syringe is placed in crushed ice unless the blood specimen is



**TABLE 20-4** 

## Bronchoscopic Abnormalities and Their Clinical Correlations

#### **ABNORMALITY**

#### Trachea

Hyperemia, loss of normal vascular pattern, excess mucus, exudate

Redundant tracheal membrane Flattened cartilage rings Uniform narrowing Strictures

Mass lesions Tears

#### Carina

Widened Multiple raised nodules Foreign body

#### Bronchi

Hyperemia, excess mucus, exudate
Collapse of airway during expiration
Collapse of airway, inspiration and expiration, ability
to pass scope through narrowed airway
Collapse of airway, inspiration and expiration, inability
to pass scope through narrowed airway
Collapse of airway with "puckering" of mucosa
Hemorrhage

Single mass lesion Multiple polypoid masses Foreign body

## CLINICAL CORRELATION

Inflammation

Tracheal collapse Tracheal collapse Hypoplastic trachea Prior trauma

Fractured rings, foreign body granuloma, neoplasia
Usually caused by excessive endotracheal tube cuff pressure

Hilar lymphadenopathy, extraluminal mass Oslerus osleri Foreign body

Inflammation

Chronic inflammation, bronchomalacia Chronic inflammation, bronchomalacia

Extraluminal mass lesions (neoplasia, granuloma, abscess)

Lung lobe torsion

Neoplasia, fungal infection, heartworm, thromboembolic disease, coagulopathy, trauma (including foreign body related)

Neoplasia

Usually chronic bronchitis; at carina, Oslerus

Foreign body



#### FIG 20-28

Position for obtaining an arterial blood specimen from the femoral artery. The dog is in left lateral recumbency. The right rear limb is being held perpendicular to the table to expose the left inguinal area. The pulse is palpated in the femoral triangle between two fingers to accurately locate the artery. The needle is laid directly on top of the artery, then stabbed into it with a short, jabbing motion.

to be analyzed immediately. Specimens should be analyzed as soon as possible after collection. Minimal alterations occur in specimens stored on ice during the few hours required to transport the specimen to a human hospital if a blood gas analyzer is not available on site. Because of the availability of reasonably priced blood gas analyzers, point-of-care testing is now possible.

## INTERPRETATION OF RESULTS

Approximate arterial blood gas values for normal dogs and cats are provided in Table 20-5. More exact values should be obtained for normal dogs and cats using the actual analyzer.

## Pao<sub>2</sub> and Paco<sub>2</sub>

Abnormal PaO<sub>2</sub> and PaCO<sub>2</sub> values can result from technical error. The animal's condition and the collection technique are considered in the interpretation of blood gas values. For example, an animal in stable condition with normal mucous membrane characteristics being evaluated for exercise intolerance is unlikely to have a resting PaO<sub>2</sub> of 45 mm Hg. The



FIG 20-29

Position for obtaining an arterial blood specimen from the dorsal pedal artery. The dog is in left lateral recumbency, with the medial surface of the left leg exposed. A pulse is palpated just below the tarsus on the dorsal surface of the metatarsus between the midline and the medial aspect of the distal limb.



**TABLE 20-5** 

Approximate Ranges of Arterial Blood Gas Values for Normal Dogs and Cats Breathing Room Air

MEASUREMENT	ARTERIAL BLOOD	
PaO <sub>2</sub> (mm Hg)	85-100	
PaCO <sub>2</sub> (mm Hg)	35-45	
HCO <sub>3</sub> (mmol/L)	21-27	
рН	7.35-7.45	

collection of venous blood is a more likely explanation for this abnormal value.

Hypoxemia is present if the PaO<sub>2</sub> is below the normal range. The oxyhemoglobin dissociation curve describing the relationship between the saturated hemoglobin level and

PaO<sub>2</sub> is sigmoid in shape, with a plateau at higher PaO<sub>2</sub> values (Fig. 20-30). Normal hemoglobin is almost totally saturated with oxygen when the PaO<sub>2</sub> is greater than 80 to 90 mm Hg, and clinical signs are unlikely in animals with such values. The curve begins to decrease more quickly at lower PaO<sub>2</sub> values. A value of less than 60 mm Hg corresponds to a hemoglobin saturation that is considered dangerous, and treatment for hypoxemia is indicated. (See the section on oxygen content, delivery, and utilization [p. 282] for further discussion.)

In general, animals become cyanotic when the PaO<sub>2</sub> reaches 50 mm Hg or less, which results in a concentration of nonoxygenated (unsaturated) hemoglobin of 5 g/dl or more. Cyanosis occurs as a result of the increased concentration of nonoxygenated hemoglobin in the blood and is not a direct reflection of the PaO<sub>2</sub>. The development of cyanosis depends on the total concentration of hemoglobin, as well as the oxygen pressure; cyanosis develops more quickly in animals with polycythemia than in animals with anemia. Acute hypoxemia resulting from lung disease more often produces pallor in an animal than cyanosis. Treatment for hypoxemia is indicated for all animals with cyanosis.

Determining the mechanism of hypoxemia is useful in selecting appropriate supportive therapy. These mechanisms include hypoxentilation, inequality of ventilation and perfusion within the lung, and diffusion abnormality. Hypoxentilation is the inadequate exchange of gases between the outside of the body and the alveoli. The PaO<sub>2</sub> and PaCO<sub>2</sub> are both affected by a lack of gas exchange, and hypercapnia occurs in conjunction with hypoxemia. Causes of hypoxentilation are listed in Box 20-9.

The ventilation and perfusion of different regions of the lung must be matched for the blood leaving the lung to be fully oxygenated. The relationship between ventilation (V) and perfusion (Q) can be described as a ratio (V/Q). Hypoxemia can develop if there are regions of lung with either a low or a high V/Q.

Poorly ventilated portions of lung with normal blood flow have a low V/Q. Regionally decreased ventilation occurs in most pulmonary diseases for reasons such as alveolar flooding, alveolar collapse, or small airway obstruction. The flow of blood past totally nonaerated tissue is known as a venous admixture or shunt (V/Q of zero). The alveoli may be unventilated as a result of complete filling or collapse, resulting in physiologic shunts, or the alveoli may be bypassed by true anatomic shunts. Unoxygenated blood from these regions then mixes with oxygenated blood from ventilated portions of the lung. The immediate result is a decreased PaO2 and an increased PaCO2. The body responds to the hypercapnia by increasing ventilation, effectively returning the PaCO<sub>2</sub> to normal or even lower than normal. However, the increased ventilation cannot correct the hypoxemia because blood flowing by ventilated alveoli is already maximally saturated.

Except where shunts are present, the PaO<sub>2</sub> can be improved in dogs and cats with lung regions with low V/Q by providing supplemental oxygen therapy administered by face mask,

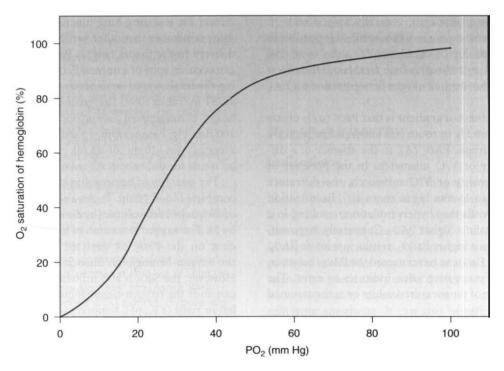


FIG 20-30 Oxygen-hemoglobin dissociation curve (approximation).



BOX 20-9

Clinical Correlations of Blood Gas Abnormalities

## Decreased PaO<sub>2</sub> and Increased PaCO<sub>2</sub> (Normal A-a Gradient)

Venous specimen

Hypoventilation

Airway obstruction

Decreased ventilatory muscle function

- Anesthesia
- Central nervous system disease
- Polyneuropathy
- Polymyopathy
- Neuromuscular junction disorders (myasthenia aravis)
- Extreme fatigue (prolonged distress)

Restriction of lung expansion

- · Thoracic wall abnormality
- Excessive thoracic bandage
- Pneumothorax
- Pleural effusion

Increased dead space (low alveolar ventilation)

 Severe chronic obstructive pulmonary disease/ emphysema

End-stage severe pulmonary parenchymal disease Severe pulmonary thromboembolism

## Decreased PaO<sub>2</sub> and Normal or Decreased PaCO<sub>2</sub> (Wide A-a Gradient)

Ventilation/perfusion (V/Q) abnormality

Most lower respiratory tract diseases (see Table 19-1,
p. 248)

oxygen cage, or nasal catheter. Positive-pressure ventilation may be necessary to combat atelectasis (see Chapter 27).

The ventilation of areas of lung with decreased circulation (a high V/Q) occurs in dogs and cats with thromboembolism. Initially there may be little effect on arterial blood gas values because blood flow is shifted to unaffected regions of the lung. However, blood flow in the normal regions of the lungs increases with increasing severity of disease, and V/Q is decreased enough in those regions that a decreased PaO<sub>2</sub> and a normal or decreased PaCO<sub>2</sub> occur, as described previously. Both hypoxemia and hypercapnia are seen in the setting of extremely severe embolization.

Diffusion abnormalities alone do not result in clinically significant hypoxemia but can occur in conjunction with V/Q mismatching in diseases such as idiopathic pulmonary fibrosis and noncardiogenic pulmonary edema. Gas is normally exchanged between the alveoli and the blood by diffusing across the respiratory membrane. This membrane consists of the fluid lining the alveolus, alveolar epithelium, alveolar basement membrane, interstitium, capillary basement membrane, and capillary endothelium. Gases must also diffuse through plasma and red blood cell membranes. Functional and structural adaptations that facilitate diffusion between the alveoli and red blood cells provide an efficient system for this process, which is rarely affected significantly by disease.

## A-a Gradient

Hypoventilation is differentiated from  $\dot{V}/\dot{Q}$  abnormalities by evaluating the PaCO<sub>2</sub> in conjunction with the PaO<sub>2</sub>. Qualitative differences are described in the preceding paragraphs: hypoventilation is associated with hypoxemia and hypercap-

nia, and  $\dot{V}/\dot{Q}$  abnormalities are generally associated with hypoxemia and normocapnia or hypocapnia. It is possible to quantify this relationship by calculating the alveolar-arterial oxygen gradient (*A-a* gradient), which factors out the effects of ventilation and the inspired oxygen concentration on PaO<sub>2</sub> (Table 20-6).

The premise of the A-a gradient is that  $PaO_2$  (a) is nearly equal (within 10 mm Hg in room air) to the partial pressure of oxygen in the alveoli,  $PAO_2$  (A), in the absence of a diffusion abnormality or  $\dot{V}/\dot{Q}$  mismatch. In the presence of a diffusion abnormality or  $\dot{V}/\dot{Q}$  mismatch, the difference widens (greater than 15 mm Hg in room air). Examination of the equation reveals that hyperventilation, resulting in a lower  $PaCO_2$ , results in a higher  $PaCO_2$ . Conversely, hypoventilation, resulting in a higher  $PaCO_2$ , results in a lower  $PAO_2$ . Physiologically the  $PaO_2$  can never exceed the  $PAO_2$ , however, and the finding of a negative value indicates an error. The error may be in one of the measured values or in the assumed R value (see Table 20-6).

Clinical examples of the calculation and interpretation of the *A-a* gradient are provided in Box 20-10.

## Oxygen Content, Delivery, and Utilization

The commonly reported blood gas value PaO<sub>2</sub> reflects the pressure of oxygen dissolved in arterial blood. This value is

critical for assessing lung function. However, the clinician must remember that other variables are involved in oxygen delivery to the tissues besides PaO<sub>2</sub> and that tissue hypoxia can occur in spite of a normal PaO<sub>2</sub>. The formula for calculating the total oxygen content of arterial blood (CaO<sub>2</sub>) is provided in Table 20-6. The greatest contribution to CaO<sub>2</sub> in health is oxygenated hemoglobin. In a normal dog (PaO<sub>2</sub>, 100 mm Hg; hemoglobin, 15 g/dl), oxygenated hemoglobin accounts for 20 ml of O<sub>2</sub>/dl, whereas dissolved oxygen accounts for only about 0.3 ml of O<sub>2</sub>/dl.

The quantity of hemoglobin is routinely appraised by the complete blood count. It can also be estimated on the basis of the packed cell volume (by dividing the packed cell volume by 3). The oxygen saturation of hemoglobin (SaO<sub>2</sub>) is dependent on the PaO<sub>2</sub>, as depicted by the sigmoid shape of the oxygen-hemoglobin dissociation curve (see Fig. 20-30). However, the SaO<sub>2</sub> is also influenced by other variables that can shift the oxygen-hemoglobin dissociation curve to the left or right (e.g., pH, temperature, or 2,3-diphosphoglycerate concentrations) or interfere with oxygen binding with hemoglobin (e.g., carbon monoxide toxicity or methemoglobinemia). Some laboratories measure SaO<sub>2</sub>.

Oxygen must also be successfully delivered to the tissues, and this depends on cardiac output and local circulation. Ultimately, the tissues must be able to effectively utilize the



TABLE 20-6

Relationships of Arterial Blood Gas Measurements

#### **FORMULA** DISCUSSION Pao<sub>2</sub> ∝ Sao<sub>2</sub> Relationship is defined by sigmoid oxygen-hemoglobin dissociation curve. Curve plateaus at greater than 90% Sao<sub>2</sub> with Pao<sub>2</sub> values greater than 80 mm Hg. Curve is steep at Pao<sub>2</sub> values of between 20 and 60 mm Hg. (Assuming normal hemoglobin, pH, temperature, and 2,3-diphosphoglycerate concentrations.) Total oxygen content of blood is greatly influenced by Sao<sub>2</sub> and hemoglobin $Cao_2 = (Sao_2 \times Hgb \times 1.34) +$ concentration. In health, more than 60 times more oxygen is delivered by $(0.003 \times Pao_2)$ hemoglobin than is dissolved in plasma (Pao<sub>2</sub>). $Paco_2 = PAco_2$ These values are increased with hypoventilation at alveolar level and decreased with hypoventilation. $PAo_2 = Flo_2 (P_B - PH_2O) - Paco_2/R$ Partial pressure of oxygen in alveolar air available for exchange with blood on room air at sea level: PAo<sub>2</sub> = changes directly with inspired oxygen concentration and inversely with Paco<sub>2</sub>. $150 \text{ mm Hg} - \text{Paco}_2/0.8$ R is assumed to be 0.8 for fasting animals. With normally functioning lungs (minimal V/Q mismatch), alveolar hyperventilation results in increased PAo<sub>2</sub> and subsequently increased Pao<sub>2</sub>, whereas hypoventilation results in decreased PAo<sub>2</sub> and decreased Pao<sub>2</sub>. $A-a = PAo_2 - Pao_2$ A-a gradient quantitatively assesses V/Q mismatch by eliminating contribution of alveolar ventilation and inspired oxygen concentration to measured Pao<sub>2</sub>. Low Pao<sub>2</sub>, with a normal A-a gradient (10 mm Hg in room air) indicates hypoventilation alone. Low Pao2 with a wide A-a gradient (>15 mm Hg in room air) indicates a component of V/Q mismatch. Paco<sub>2</sub> ∞ 1/pH Increased Paco<sub>2</sub> causes respiratory acidosis; decreased Paco<sub>2</sub> causes respiratory alkalosis. Actual pH depends on metabolic (HCO3) status as well.

A-a, Alveolar-arterial oxygen gradient (mm Hg);  $Cao_2$ , oxygen content of arterial blood (ml of  $O_2/dl$ );  $Flo_2$ , fraction of oxygen in inspired air (%); Hgb, hemoglobin concentration (g/dl);  $Paco_2$ , partial pressure of  $CO_2$  in arterial blood (mm Hg);  $PAco_2$ , partial pressure of  $O_2$  in alveolar air (mm Hg);  $Pao_2$ , partial pressure of  $O_2$  in arterial blood (mm Hg);  $PAco_2$ , partial pressure of  $O_2$  in alveolar air (mm Hg);  $PAco_2$ , partial pressure of  $O_2$  in alveolar air (mm Hg);  $PAco_2$ , partial pressure of water in alveolar air (100% humidified) (mm Hg);  $PAco_2$ , partial pressure of water in alveolar air (100% humidified) (mm Hg);  $PAco_2$ , partial pressure of water in alveolar air (100% humidified) (mm Hg);  $PAco_2$ , partial pressure of water in alveolar air (100% humidified) (mm Hg);  $PAco_2$ , partial pressure of  $PAco_2$ , partial pressu



BOX 20-10

## Calculation and Interpretation of A-a Gradient: Clinical Examples

Example 1: A healthy dog breathing room air has a  $PaO_2$  of 95 mm Hg and a  $PaCO_2$  of 40 mm Hg. His calculated  $PAO_2$  is 100 mm Hg. ( $PAO_2 = FIO_2$  [ $P_B - PH_2O$ ]  $- PaCO_2/R = 0.21$  [765 mm Hg - 50 mm Hg] - [40 mm Hg/0.8].] The A-a gradient is 100 mm Hg - 95 mm Hg = 5 mm Hg. This value is normal.

Example 2: A dog with respiratory depression due to an anesthetic overdose has a PaO<sub>2</sub> of 72 mm Hg and a PaCO<sub>2</sub> of 56 mm Hg in room air. His calculated PAO<sub>2</sub> is 80 mm Hg. The A-a gradient is 8 mm Hg. His hypoxemia can be explained by hypoventilation.

Later the same day, the dog develops crackles bilaterally. Repeat blood gas analysis shows a PaO<sub>2</sub> of 60 mm Hg and a PaCO<sub>2</sub> of 48 mm Hg. His calculated PAO<sub>2</sub> is 90 mm Hg. The A-a gradient is 30 mm Hg. Hypoventilation continues to contribute to the hypoxemia, but hypoventilation has improved. The widened A-a gradient indicates V/Q mismatch. This dog has aspirated gastric contents into his lungs.

oxygen—a process interfered with in the presence of toxicities such as carbon monoxide or cyanide poisoning. Each of these processes must be considered when interpreting the blood gas values in an individual animal.

## **Acid-Base Status**

The acid-base status of an animal can also be assessed using the same blood sample as that used to measure blood gases. Acid-base status is influenced by the respiratory system (see Table 20-6). Respiratory acidosis results if carbon dioxide is retained as a result of hypoventilation. If the problem persists for several days, compensatory retention of bicarbonate by the kidneys occurs. Excess removal of carbon dioxide by the lungs caused by hyperventilation results in respiratory alkalosis. Hyperventilation is usually an acute phenomenon, potentially caused by shock, sepsis, severe anemia, anxiety, or pain; therefore compensatory changes in the bicarbonate concentration are rarely seen.

The respiratory system partially compensates for primary metabolic acid-base disorders, and this can occur quickly. Hyperventilation and a decreased PaCO<sub>2</sub> occur in response to metabolic acidosis. Hypoventilation and an increased PaCO<sub>2</sub> occur in response to metabolic alkalosis.

In most cases, acid-base disturbances can be identified as primarily respiratory or primarily metabolic in nature on the basis of the pH. The compensatory response will never be excessive and alter the pH beyond normal limits. An animal with acidosis (pH of less than 7.35) has a primary respiratory acidosis if the PaCO<sub>2</sub> is increased and a compensatory respiratory response if the PaCO<sub>2</sub> is decreased. An animal with alkalosis (pH of greater than 7.45) has a primary respiratory alkalosis if the PaCO<sub>2</sub> is decreased and a compensatory respiratory response if the PaCO<sub>2</sub> is increased.

If both the  $PaCO_2$  and the bicarbonate concentration are abnormal, such that both contribute to the same alteration in pH, a mixed disturbance is present. For instance, an animal with acidosis, an increased  $PaCO_2$ , and a decreased  $HCO_3$  has a mixed metabolic and respiratory acidosis.

## **PULSE OXIMETRY**

#### **Indications**

Pulse oximetry is a method of monitoring the oxygen saturation of blood. The saturation of hemoglobin with oxygen is related to the PaO<sub>2</sub> by the sigmoid oxygen-hemoglobin dissociation curve (see Fig. 20-30). Pulse oximetry is noninvasive, can be used to continuously monitor a dog or cat, provides immediate results, and is affordable for most practices. It is a particularly useful device for monitoring animals with respiratory disease that must undergo procedures requiring anesthesia. It can also be used in some cases to monitor the progression of disease or the response to therapy. More and more clinicians are using these devices for the routine monitoring of animals under general anesthesia, particularly if the number of personnel is limited, because alarms can be set to warn of marked changes in values.

#### METHODOLOGY

Most pulse oximeters have a probe that is attached to a fold of tissue, such as the tongue, lip, ear flap, inguinal skin fold, toe, or tail (Fig. 20-31). This probe measures light absorption through the tissues. Other models measure reflected light and can be placed on mucous membranes or within the esophagus or rectum. Artifacts resulting from external light sources are minimized in the latter sites. Arterial blood is identified by the oximeter as that component which changes in pulses. Nonpulsatile absorption is considered background.

### INTERPRETATION

Values provided by the pulse oximeter must be interpreted with care. The instrument must record a pulse that matches the palpable pulse of the animal. Any discrepancy between the actual pulse and the pulse received by the oximeter indicates an inaccurate reading. Common problems that can interfere with the accurate detection of pulses include the position of the probe, animal motion (e.g., respirations, shivering), and weak or irregular pulse pressures (e.g., tachycardia, hypovolemia, hypothermia, arrhythmias).

The value measured indicates the saturation of hemoglobin in the local circulation. However, this value can be affected by factors other than pulmonary function, such as vasoconstriction, low cardiac output, and the local stasis of blood. Other intrinsic factors that can affect oximetry readings include anemia, hyperbilirubinemia, carboxyhemoglobinemia, and methemoglobinemia. External lights and the location of the probe can also influence results. Pulse oximetry readings of oxygen saturation are less accurate below values of 80%.

These sources for error should not discourage the clinician from using this technology, however, because changes



FIG 20-31
Monitoring oxygen saturation in a cat under general anesthesia using a pulse oximeter with a probe (P) clamped on the tongue (T).

in saturation in an individual animal provide valuable information. Rather, results must be interpreted critically.

The examination of the oxygen-hemoglobin dissociation curve (see Fig. 20-30) in normal dogs and cats shows that animals with PaO<sub>2</sub> values exceeding 85 mm Hg will have a hemoglobin saturation greater than 95%. If PaO<sub>2</sub> values decrease to 60 mm Hg, the hemoglobin saturation will be approximately 90%. Any further decrease in PaO2 results in a precipitous decrease in hemoglobin saturation, illustrated by the steep portion of the oxygen-hemoglobin dissociation curve. Ideally, then, hemoglobin saturation should be maintained at more than 90% by means of oxygen supplementation or ventilatory support (see Chapter 27) or the specific treatment of the underlying disease. However, because of the many variables associated with pulse oximetry, such strict guidelines are not always valid. In practice, a baseline hemoglobin saturation value is measured and subsequent changes in that value are then used to assess improvement or deterioration in oxygenation. Ideally, the baseline value is compared with the PaO<sub>2</sub> obtained from an arterial blood sample collected concurrently to ensure the accuracy of the readings.

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## CHAPTER OUTLINE

GENERAL CONSIDERATIONS
CANINE INFECTIOUS TRACHEOBRONCHITIS
CANINE CHRONIC BRONCHITIS

General Management
Drug Therapies
Management of Complications
FELINE BRONCHITIS (IDIOPATHIC)

Emergency Stabilization
Environment
Glucocorticoids
Bronchodilators
Other Potential Treatments
Failure to Respond
COLLAPSING TRACHEA AND
TRACHEOBRONCHOMALACIA
ALLERGIC BRONCHITIS
OSLERUS OSLERI

## **GENERAL CONSIDERATIONS**

Common diseases of the trachea and bronchi include canine infectious tracheobronchitis, canine chronic bronchitis, feline bronchitis, collapsing trachea, and allergic bronchitis. *Oslerus osleri* infection is an important consideration in young dogs.

Other diseases may involve the airways, either primarily or concurrently with pulmonary parenchymal disease. These diseases, such as viral, mycoplasmal, and bacterial infection; other parasitic infections; and neoplasia are discussed in Chapter 22. Feline bordetellosis can cause signs of bronchitis (e.g., cough) but is more often associated with signs of upper respiratory disease (see the section on feline upper respiratory infection, in Chapter 15) or bacterial pneumonia (see the section on bacterial pneumonia, in Chapter 22). Dogs with mild canine influenza virus infec-

tions have acute cough and often nasal discharge. This form of the disease is similar to canine infectious tracheobronchitis and is self-limiting. The severe form of the disease is characterized by pneumonia. Canine influenza is discussed in Chapter 22.

## CANINE INFECTIOUS TRACHEOBRONCHITIS

## Etiology

Canine infectious tracheobronchitis, or "kennel cough," is a highly contagious, acute disease that is localized in the airways. One or more infectious agents cause it, including canine adenovirus 2 (CAV2), parainfluenza virus (PIV), canine respiratory coronavirus and *Bordetella bronchiseptica*. *Bordetella* organisms infect ciliated respiratory epithelium (Fig. 21-1) and can decrease mucociliary clearance. Other organisms may become involved as secondary pathogens. In most dogs the disease is self-limiting, with resolution of clinical signs in approximately 2 weeks.

## **Clinical Features**

Affected dogs are first seen because of the sudden onset of a severe productive or nonproductive cough, which is often exacerbated by exercise, excitement, or the pressure of the collar on the neck. Palpating the trachea easily induces the cough. Gagging, retching, or nasal discharge can also occur. A recent history (i.e., within 2 weeks) of boarding, hospitalization, or exposure to a puppy or dog that has similar signs is common. Puppies recently obtained from pet stores, kennels, or shelters have often been exposed to the pathogens.

The majority of dogs with infectious tracheobronchitis are considered to have "uncomplicated," self-limiting disease and do not show signs of systemic illness. Therefore dogs showing respiratory distress, weight loss, persistent anorexia, or signs of involvement of other organ systems, such as diarrhea, chorioretinitis, or seizures, may have some other, more serious disease, such as canine distemper, severe canine

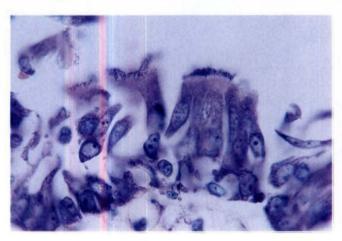


FIG 21-1
Photomicrograph of a tracheal biopsy from a dog infected with Bordetella bronchiseptica. The organisms are small basophilic rods that are visible along the ciliated border of the epithelial cells. (Giemsa stain courtesy D. Malarkey.)

influenza, or a mycotic infection. Although uncommon, serious respiratory complications can result from infectious tracheobronchitis. Secondary bacterial pneumonia can develop, particularly in puppies, immunocompromised dogs, and dogs that have preexisting lung abnormalities such as chronic bronchitis. Dogs with chronic airway disease or tracheal collapse can experience an acute, severe exacerbation of their chronic problems, and extended management may be necessary to resolve the signs associated with infection in these animals. *Bordetella* infection has been associated with canine chronic bronchitis.

#### Diagnosis

Uncomplicated cases of kennel cough are diagnosed on the basis of the presenting signs. However, differential diagnoses should also include the early presentation of a more serious disease and the mild form of canine influenza. Diagnostic testing is indicated for dogs with systemic, progressive, or unresolving signs. Tests to be considered include thoracic radiographs, a complete blood count (CBC), tracheal wash fluid analysis, and polymerase chain reaction (PCR) testing, paired serology, or other tests for canine influenza (see p. 302) and other respiratory pathogens. Tracheal wash fluid cytology shows acute inflammation, and bacterial culture of the fluid can be useful for identifying any bacteria involved in the disease. Concurrent antibiotic sensitivity information is helpful in selecting antibiotics.

#### **Treatment**

Uncomplicated infectious tracheobronchitis is a self-limiting disease. Rest for at least 7 days, specifically avoiding exercise and excitement, is indicated to minimize the continual irritation of the airways caused by excessive coughing. Cough suppressants are valuable for the same reason but should not be given if the cough is productive or if exudate is suspected to be accumulating in the lungs on the basis of auscultation



Common Cough Suppressants for Use in Dogs\*

AGENT	DOSAGE
Dextromethorphan <sup>†</sup>	1 to 2 mg/kg, q6-8h orally
Butorphanol	0.5 mg/kg, q6-12h orally
Hydrocodone bitartrate	0.25 mg/kg, q6-12h orally

\*Centrally acting cough suppressants are rarely, if ever, indicated for use in cats and can result in adverse reactions. The preceding dosages are for dogs only.

†Efficacy is questionable in dogs.

or thoracic radiograph findings. As discussed in Chapter 19 it is not always possible to recognize a productive cough in dogs. Therefore cough suppressants should be used judiciously to treat frequent or severe cough, allow for restful sleep, and prevent exhaustion.

A variety of cough suppressants can be used in dogs (Table 21-1). Dextromethorphan is available in over-the-counter preparations; however, it has questionable efficacy in dogs. Cold remedies with additional ingredients such as antihistamines and decongestants should be avoided. Pediatric liquid preparations are palatable for most dogs, and the alcohol contained in them may also have a mild tranquilizing effect. Narcotic cough suppressants are more likely to be effective. Butorphanol is available as a veterinary labeled product (Torbutrol, Fort Dodge Animal Health). Hydrocodone bitartrate is a potent alternative for dogs with refractory cough.

In theory, antibiotics are not indicated for most dogs with infectious tracheobronchitis for two reasons: (1) The disease is usually self-limiting and tends to resolve spontaneously, regardless of any specific treatment that is implemented, and (2) no antibiotic protocol has been proven to eliminate Bordetella organisms from the airways. In practice, however, antibiotics are often prescribed, and their use is justified because of the potential role of Bordetella in the disease. Fluoroquinolones have the advantage of reaching high concentrations in the airway secretions, but their use is ideally reserved for more serious infections. Other antibiotics that are effective against many Bordetella isolates include amoxicillin with clavulanate (20 to 25 mg/kg q8h), doxycycline (5 to 10 mg/kg q12h, followed by a bolus of water), and chloramphenicol (50 mg/kg q8h). Beta-lactam antibiotics do not generally reach therapeutic concentrations in airway secretions of healthy (not inflamed) subjects. If such an antibiotic is used for bronchial infections, the high end of the dosage range should be used and the drug administered every 8 hours. The ability of doxycycline to reach therapeutic concentration within the airways is questionable because in the dog it is highly protein bound, although the presence of inflammatory cells may increase locally available concentrations of the drug. Bacterial susceptibility data from tracheal wash fluid can be used to guide the selection of an

appropriate antibiotic. Antibiotics are administered for 5 days beyond the time the clinical signs resolve or for at least 14 days.

Administration of gentamicin by nebulization can be considered for refractory cases or in outbreaks of infection involving dogs housed together, although no controlled studies have been published. An early study by Bemis et al. (1997) showed that bacterial populations of Bordetella in the trachea and bronchi were reduced for up to 3 days after treatment with nebulized gentamicin but not orally administered antibiotics, and clinical signs were reduced. Note that the numbers of organisms returned to pretreatment values within 7 days. Some clinicians have since reported success in managing difficult cases and outbreaks with this treatment (Miller et al., 2003). The protocol used by Bemis et al. (1997) is 50 mg of gentamicin sulfate in 3 ml of sterile water, delivered by nebulizer and face mask (see Fig. 22-1) for 10 minutes every 12 hours for 3 days. Sterile technique must be maintained to keep from delivering additional bacteria to the airways. Nebulization of drugs has the potential to induce bronchospasms, so dogs should be carefully observed during the procedure. Pretreatment with bronchodilators should be considered, and additional bronchodilators (metered dose inhaler and/or injectable) should be at hand for use as needed.

Glucocorticoids should not be used. A field trial conducted by Thrusfield et al. (1991) failed to demonstrate any benefit of steroid therapy, either alone or in combination with antibiotics.

If clinical signs have not resolved within 2 weeks, further diagnostic evaluation is indicated. See Chapter 22 for the management of complicated cases of infectious tracheobronchitis with bacterial pneumonia.

#### **Prognosis**

The prognosis for recovery from uncomplicated infectious tracheobronchitis is excellent.

### **Prevention**

Canine infectious tracheobronchitis can be prevented by minimizing an animal's exposure to organisms and through vaccination programs. Excellent nutrition, routine deworming, and avoidance of stress improve the dog's ability to respond appropriately to infection without showing serious signs.

Bordetella may persist in the airways of dogs for up to 3 months after infection. To minimize exposure to Bordetella or respiratory viruses, dogs are kept isolated from puppies or dogs that have been recently boarded. Careful sanitation should be practiced in kenneling facilities. Caretakers should be instructed in the disinfection of cages, bowls, and runs, and anyone working with the dogs must wash their hands after handling each animal. Dogs should not be allowed to have face-to-face contact. Adequate air exchange and humidity control are necessary in rooms housing several dogs. Recommended goals are at least 10 to 15 air exchanges per hour and less than 50% humidity. An isolation area is essen-

tial for the housing of dogs with clinical signs of infectious tracheobronchitis.

Injectable and intranasal vaccines are available for the three major pathogens involved in canine infectious tracheobronchitis (i.e., CAV2, PIV, *B. bronchiseptica*). Injectable modified-live virus vaccines against CAV2 and PIV are adequate for most pet dogs. They are conveniently included in most combination distemper vaccines. Because maternal antibodies interfere with the response to the vaccines, puppies must be vaccinated every 2 to 4 weeks, beginning at 6 to 8 weeks of age and through 14 to 16 weeks of age. At least two vaccines must be given initially. For most healthy dogs, a booster is recommended after 1 year, followed by subsequent vaccinations every 3 years (see Chapter 94).

Dogs at high risk for disease, such as those in kennels where the disease is endemic or those that are frequently boarded, may benefit from vaccines incorporating B. bronchiseptica. These vaccines do not prevent infection but aim to decrease clinical signs if infection occurs. They may also reduce the duration of shedding of organisms after infection. A study by Ellis et al. (2001) indicated that both intranasal and parenteral Bordetella vaccines afford similar protection based on antibody titers, clinical signs, upper airway cultures, and histopathologic examination of tissues after exposure to organisms. The greatest benefit was achieved by administering both forms of vaccine sequentially at a 2-week interval. Unfortunately, the parenteral vaccine used in the study was a killed bacterin that is no longer available. The dogs in this study were vaccinated between 14 to 18 weeks of age. Also in experimental settings, protection against challenge following intranasal vaccination against B. bronchiseptica and PIV began by 72 hours after vaccination and persisted for at least 13 months (Gore et al., 2005; Jacobs et al., 2005). Intranasal Bordetella vaccines occasionally cause clinical signs, predominantly cough. The signs are generally self-limiting but are disturbing to most owners.

### CANINE CHRONIC BRONCHITIS

## Etiology

Canine chronic bronchitis is a disease syndrome defined as cough occurring on most days of 2 or more consecutive months in the past year in the absence of other active disease. Histologic changes of the airways are those of long-term inflammation and include fibrosis, epithelial hyperplasia, glandular hypertrophy, and inflammatory infiltrates. Some of these changes are irreversible. Excessive mucus is present within the airways, and small airway obstruction occurs. In people chronic bronchitis is strongly associated with smoking. It is presumed that canine chronic bronchitis is a consequence of a long-standing inflammatory process initiated by infection, allergy, or inhaled irritants or toxins. A continuing cycle of inflammation likely occurs as mucosal damage, mucus hypersecretion, and airway obstruction

impairs normal mucociliary clearance, and inflammatory mediators amplify the response to irritants and organisms.

#### **Clinical Features**

Chronic bronchitis occurs most often in middle-aged or older, small-breed dogs. Breeds commonly affected include Terriers, Poodles, and Cocker Spaniels. Small-breed dogs are also predisposed to the development of collapsing trachea and mitral insufficiency with left atrial enlargement causing compression of the mainstem bronchi. These causes for cough must be differentiated, and their contribution to the development of the current clinical features determined, for appropriate management to be implemented.

Dogs with chronic bronchitis are evaluated because of loud, harsh cough. Mucus hypersecretion is a component of the disease, but the cough may sound productive or nonproductive. The cough has usually progressed slowly over months to years, although clients usually report the initial onset as acute. There should be no systemic signs of illness such as anorexia or weight loss. As the disease progresses, exercise intolerance becomes evident; then incessant coughing or overt respiratory distress is seen.

Potential complications of chronic bronchitis include bacterial or mycoplasmal infection, tracheobronchomalacia (see p. 297), pulmonary hypertension (Chapter 22), and bronchiectasis. *Bronchiectasis* is the term for permanent dilation of the airways (Fig. 21-2; see also Fig. 20-4). Bronchiectasis can be present secondary to other causes of chronic airway inflammation, airway obstruction, and in association with certain congenital disorders such as ciliary dyskinesia (i.e., immotile cilia syndrome). Bronchiectasis caused by traction on the airways, rather than bronchial disease, can be seen with idiopathic pulmonary fibrosis. Generally, all the major airways are dilated in dogs with bronchiectasis, but occasionally it is localized. Recurrent bacterial infections and overt bacterial pneumonia are common complications in dogs with bronchiectasis.

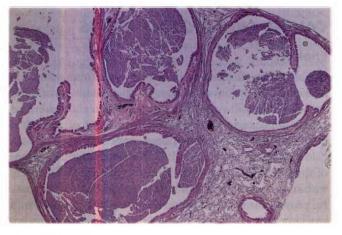


FIG 21-2
Photomicrograph of a lung biopsy from a dog with severe bronchiectasis. The airways are filled with exudate and are greatly dilated (H&E stain).

Dogs with chronic bronchitis are often brought to a veterinarian because of sudden exacerbation of signs. The change in signs may result from transient worsening of the chronic bronchitis, perhaps after a period of unusual excitement, stress, or exposure to irritants or allergens; from a secondary complication, such as bacterial infection; or from the development of a concurrent disease, such as left atrial enlargement and bronchial compression or heart failure (Box 21-1). In addition to obtaining a routine complete history, the client should be carefully questioned about the character of the cough and the progression of signs. Detailed information should be obtained regarding the following: environmental conditions, particularly exposure to smoke, other potential irritants and toxins, or allergens; exposure to infectious agents, such as boarding or exposure to puppies; and all previous and current medications and the response to treatment.

On physical examination, increased breath sounds, crackles, or occasionally wheezes are auscultated in animals with chronic bronchitis. End-expiratory clicks caused by mainstem bronchial or intrathoracic tracheal collapse may be heard in animals with advanced disease. A prominent or split second heart sound occurs in animals with secondary pulmonary hypertension. Dogs with respiratory distress (end-stage disease) characteristically show marked expiratory efforts because of the narrowing and collapse of the intrathoracic



## BOX 21-1

Bacterial infection

Diagnostic Considerations for Dogs with Signs Consistent with Canine Chronic Bronchitis

## Other Active Disease (Rather than Canine Chronic Bronchitis)

Mycoplasmal infection
Bronchial compression (e.g., left atrial enlargement)
Pulmonary parasites
Heartworm disease
Allergic bronchitis
Neoplasia
Foreign body
Chronic aspiration
Gastroesophageal reflux\*

#### **Potential Complications of Canine Chronic Bronchitis**

Tracheobronchomalacia Pulmonary hypertension Bacterial infection Mycoplasmal infection Bronchiectasis

### **Most Common Concurrent Cardiopulmonary Diseases**

Collapsing trachea
Bronchial compression (e.g., left atrial enlargement)
Heart failure

<sup>\*</sup>Gastroesophageal reflux is a common cause of chronic cough in people. Documentation in dogs and cats is limited.

large airways. The presence of a fever or other systemic signs is suggestive of other disease, such as bacterial pneumonia.

## **Diagnosis**

Canine chronic bronchitis is defined as a cough occurring on most days of 2 or more consecutive months in the past year *in the absence of other active disease*. Therefore chronic bronchitis is diagnosed on the basis of not only clinical signs but also the elimination of other diseases from the list of differential diagnoses (see Box 21-1). The possibility of secondary disease complicates this simple definition.

A bronchial pattern with increased interstitial markings is typically seen on thoracic radiographs, but changes are often mild and difficult to distinguish from clinically insignificant changes associated with aging. In a study by Mantis et al. (1998), thoracic radiographs had a sensitivity of 50% to 65% for the diagnosis of chronic bronchitis. Thoracic radiographs are most useful for ruling out other active disease and identifying concurrent or secondary disease.

Tracheal wash or bronchoalveolar lavage (BAL) fluid should be collected at the time of the initial presentation and after a persistent exacerbation of signs. Neutrophilic or mixed inflammation and increased amounts of mucus are usually present. The finding of degenerative neutrophils indicates the possibility of a bacterial infection. Although not a specific finding, airway eosinophilia is suggestive of a hypersensitivity reaction, as can occur with allergy, parasitism, or heartworm disease. Slides should be carefully examined for organisms. Bacterial cultures are performed and the results interpreted as discussed in Chapter 20. Although the role of *Mycoplasma* infections in these cases is not well understood, *Mycoplasma* cultures are also considered.

Bronchoscopy, with specimen collection, is performed in selected cases, primarily to help rule out other diseases. The maximal benefit of bronchoscopy is obtained early in the course of disease, before severe permanent damage has occurred and while the risk of the procedure is minimal. Gross abnormalities visualized by bronchoscopy include an increased amount of mucus, roughened mucosa, and hyperemia. Major airways may collapse during expiration as a result of weakened walls (Fig. 21-3), and polypoid mucosal proliferation may be present. Bronchial dilatation is seen in animals with bronchiectasis.

Further diagnostic procedures are indicated to rule out other potential causes of chronic cough, and the selection of these depends on the presenting signs and the results of the previously discussed diagnostic tests. Diagnostic tests to be considered include heartworm tests, fecal examinations for pulmonary parasites, echocardiography, and systemic evaluation (i.e., CBC, serum biochemical panel, urinalysis). Echocardiography may reveal evidence of secondary pulmonary hypertension, including right heart enlargement (i.e., cor pulmonale).

Ciliary dyskinesia, in which ciliary motion is abnormal, is uncommon but should be considered in young dogs with bronchiectasis or recurrent bacterial infection. Abnormalities exist in all ciliated tissues, and situs inversus (i.e., lateral

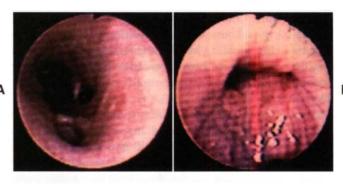


FIG 21-3
Bronchoscopic view of the right caudal bronchus of a dog with chronic bronchitis and severe bronchomalacia. The airways appear normal during inspiration (A) but completely collapse during expiration, obliterating the lumen of the airway (B).

transposition of the abdominal and thoracic organs, such that left-sided structures are found on the right and vice versa) is seen in 50% of such dogs. Dextrocardia occurring in association with chronic bronchitis is extremely suggestive of this disease. Sperm motility can be evaluated in intact male dogs. The finding of normal sperm motility rules out a diagnosis of ciliary dyskinesia. The disease is diagnosed on the basis of the rate at which radioisotopes deposited at the carina are cleared and the findings from electron microscopic examination of bronchial biopsy, nasal biopsy, or sperm specimens.

#### **Treatment**

Chronic bronchitis is managed symptomatically, with specific treatment possible only for concurrent or complicating diseases that are identified. Each dog with chronic bronchitis is presented at a different stage of the disease, with or without concurrent or secondary cardiopulmonary disease (see Box 21-1). Hence each dog must be managed individually. Ideally, medications are initiated one at a time to assess the most effective combination. It will likely be necessary to modify treatment over time.

## **GENERAL MANAGEMENT**

Exacerbating factors, either possible or proven, are avoided. Potential allergens are considered in dogs with eosinophilic inflammation and trial elimination pursued (see the section on allergic bronchitis, p. 299). Exposure to irritants such as smoke (from tobacco or fireplace) and perfumed products should be avoided in all dogs. Motivated clients can take steps to improve the air quality in their home, such as carpet, furniture, and drapery cleaning; cleaning of the furnace and the frequent replacement of air filters; and the use of an air cleaner. The American Lung Association has a useful Web site with nonproprietary recommendations for improving indoor air quality (www.lungusa.org ). Excitement or stress can cause an acute worsening of signs in some animals, and short-term tranquilization with acepromazine or sedation with phenobarbital can be helpful in relieving the signs.

It is normal for flora from the oropharynx to be aspirated into the airways. Routine dental prophylaxis and teeth brushing will help maintain a healthy oral flora and may decrease any contributions of normal aspiration to ongoing airway inflammation in these patients with reduced mucociliary clearance.

Airway hydration should be maintained to facilitate mucociliary clearance. Adequate airway hydration is best achieved by maintaining systemic hydration. Therefore diuretic therapy is not recommended in these patients. For severely affected dogs, placing the animal in a steamy bathroom or in a room with a vaporizer daily may provide symptomatic relief, although the moisture does not penetrate very deeply into the airways. Nebulization of saline will allow moisture to go more deeply in the lungs. This technique is discussed further in the section on bacterial pneumonia in Chapter 22.

Patients that are overweight and/or unfit may benefit from weight loss (Chapter 54) and exercise. Exercise should be tailored to the dog's current fitness level and degree of pulmonary dysfunction to keep from causing excessive respiratory efforts or even death. Observing the dog during specific exercise, such as a short walk, while in the client's presence may be necessary to make initial recommendations. Instructing clients in the measurement of respiratory rate, observation of mucous membrane color, and signs of increased respiratory effort will improve their ability to assess their dog's status during exercise.

## DRUG THERAPIES

Medications to control clinical signs include bronchodilators, glucocorticoids, and cough suppressants.

Theophylline, a methylxanthine bronchodilator, has been used for years for the treatment of chronic bronchitis in people and dogs. This drug became unpopular with physicians when newer bronchodilators with fewer side effects became available. However, recent research in people suggests that theophylline is effective in treating the underlying inflammation of chronic bronchitis, even at concentrations below those resulting in bronchodilation (hence, reducing side effects), and that the antiinflammatory effects may be synergistic with those of glucocorticoids. Theophylline may also improve mucociliary clearance, decrease fatigue of respiratory muscles, and inhibit the release of mast cell mediators of inflammation. The potential beneficial effects of theophylline beyond bronchodilation may be of particular importance in dogs because their airways are not as reactive (i.e., likely to bronchospasm) as those of cats and people. However, theophylline alone is rarely sufficient to control the clinical signs of chronic bronchitis.

Other advantages of theophylline are the availability of long-acting preparations that can be administered twice daily to dogs and the fact that plasma concentrations of drug can be easily measured by commercial diagnostic laboratories. A disadvantage of theophylline is that other drugs, such as fluoroquinolones and chloramphenicol, can delay its clearance and cause signs of theophylline toxicity if the

dosage is not reduced by one third to one half. Potential adverse effects include gastrointestinal signs, cardiac arrhythmias, nervousness, and seizures. Serious adverse effects are extremely rare at therapeutic concentrations.

Variability in sustained plasma concentrations has been found for different long-acting theophylline products. Dosage recommendations are currently available for a generic product from a specific manufacturer (Box 21-2). If beneficial effects are not seen, the patient is predisposed to adverse effects, or adverse effects occur, plasma theophylline concentrations should be measured. Therapeutic peak concentrations for bronchodilation, based on data from people, are 5 to 20 µg/ml. Plasma is collected during peak concentrations, generally 4 to 5 hours after administration of a long-acting product or 1.5 to 2 hours after administration of immediate release products. Measurement of concentrations immediately before the next scheduled dose might provide useful information concerning duration of therapeutic concentrations.

Theophylline and related drugs that are not long acting are useful in specific circumstances but must be administered three times daily (see Box 21-2). Palatable elixirs of



Common Bronchodilators for Use in Dogs and Cats

### Methylxanthines

Aminophylline

Cat: 5 mg/kg orally q12h Dog: 11 mg/kg orally q8h

Oxtriphylline elixir (Choledyl, Parke-Davis)

Cat: None

Dog: 14 mg/kg orally q8h

Theophylline base (immediate release)

Cat: 4 mg/kg orally q12h Dog: 9 mg/kg orally q8h

Long-acting theophylline (Theochron or TheoCap, Inwood

Laboratories, Inwood, NY)\*
Cat: 15 mg/kg q24h, in evening

Dog: 10 mg/kg q12h

## **Sympathomimetics**

Terbutaline

Cat: 1/8-1/4 of 2.5 mg tablet/cat orally q12h; or 0.01 mg/kg subcutaneously; can repeat once

Dog: 1.25-5 mg/dog orally q8-12h

Albuterol

Cat and Dog: 20-50 µg/kg orally q8-12h (0.02-0.05 mg/kg), beginning with lower dose.

\*Canine dosage for these products from Inwood Laboratories from Bach JF et al: Evaluation of the bioavailability and pharmacokinetics of two extended-release theophylline formulations in dogs, J Am Vet Med Assoc 224:1113, 2004. Feline dosage from Guenther-Yenke CL et al: Pharmacokinetics of an extended-release theophylline product in cats. J Am Vet Med Assoc 231:900, 2007. Monitoring of plasma concentrations is recommended in patients at risk for or with signs of toxicity and in patients that fail to respond to treatment.

theophylline derivatives (e.g., oxtriphylline) are convenient for administration to toy breeds. Therapeutic blood concentrations are reached more quickly after the administration of liquids, or tablets or capsules that are not long acting.

Sympathomimetic drugs are preferred by some clinicians as bronchodilators (see Box 21-2). Terbutaline and albuterol are selective for  $\beta_2$ -adrenergic receptors, lessening their cardiac effects. Potential adverse effects include nervousness, tremors, hypotension, and tachycardia. The clinical use of bronchodilators delivered by metered-dose inhaler, such as albuterol and ipatropium (a parasympatholytic), has not been reported in dogs with chronic bronchitis.

Glucocorticoids are often effective in controlling the signs of chronic bronchitis and may slow the development of permanent airway damage by decreasing inflammation. They may be particularly helpful in dogs with eosinophilic airway inflammation. Potential negative effects include an increased susceptibility to infection in dogs already impaired by decreased airway clearance; a tendency toward obesity, hepatomegaly, and muscle weakness that may adversely affect ventilation; and pulmonary thromboembolism. Therefore short-acting products are used, the dose is tapered to the lowest effective one (when possible, 0.5 mg/kg q48h or less), and the drug is discontinued if no beneficial effect is seen. Prednisone is initially given at a dose of 0.5 to 1.0 mg/kg every 12 hours, with a positive response expected within 1 week.

Dogs that require relatively high dosages of prednisone, have unacceptable adverse effects, or have conditions for which glucocorticoids are relatively contraindicated (e.g., diabetes mellitus) may benefit from local treatment with metered-dose inhalers. This route of administration is discussed in more detail later in this chapter, in the section on feline bronchitis (p. 295).

Cough suppressants are used cautiously because cough is an important mechanism to clear airway secretions. In some dogs, however, the cough is incessant and exhausting, or ineffective because of marked tracheobronchomalacia and airway collapse. Cough suppressants can provide significant relief in such animals and may even facilitate ventilation and decrease anxiety.

Although the doses given in Table 21-1 are the ones that provide prolonged effectiveness, less frequent administration (i.e., only during times of the day when coughing is most severe) may preserve some beneficial effect of cough. For dogs with severe cough, hydrocodone may provide the greatest relief.

#### MANAGEMENT OF COMPLICATIONS

Antibiotics are often prescribed for dogs with chronic bronchitis. If possible, confirmation of infection and antibiotic sensitivity information should be obtained by culture of an airway specimen (e.g., tracheal wash fluid). Because cough in dogs with chronic bronchitis often waxes and wanes in severity, it is difficult to make a diagnosis of infection on the basis of the patient's response to therapy. Furthermore,

organisms involved in bronchial infections generally originate from the oropharynx. They are frequently gramnegative with unpredictable antibiotic sensitivity patterns. The role of *Mycoplasma* organisms in canine chronic bronchitis is not well understood. They may be an incidental finding or pathogenic. Ideally, antibiotic selection is based on results of culture. Antibiotics that are generally effective against *Mycoplasma* include doxycycline, azithromycin, chloramphenicol, and fluoroquinolones.

In addition to the susceptibility of identified organisms, the ability of selected antibiotics to penetrate the airway secretions to the site of infection should be considered when selecting an antibiotic. Antibiotics that are likely to reach concentrations effective against susceptible organisms include chloramphenicol, fluoroquinolones, azithromycin, and possibly amoxicillin with clavulanate. Beta-lactam antibiotics do not generally reach therapeutic concentrations in airway secretions of healthy (not inflamed) subjects. If used for bronchial infections, the high end of the dosage range should be used and the drug administered every 8 hours (20 to 25 mg/kg q8h). Doxycycline has often been recommended because Mycoplasma and many Bordetella isolates are susceptible to this drug. However, the ability of doxycycline to reach therapeutic concentration within the airways is questionable because in the dog it is highly protein bound, although the presence of inflammatory cells may increase locally available concentrations of the drug. It is preferable to reserve fluoroquinolones for serious infections.

If an antibiotic is effective, a positive response is generally seen within 1 week. Treatment is then continued for at least 1 week beyond the time when the clinical signs stabilize because complete resolution is unlikely in these animals. Antibiotic treatment usually is necessary for 3 to 4 weeks. Even longer treatment may be necessary in some cases, particularly if bronchiectasis or overt pneumonia is present. The use of antibiotics for the treatment of respiratory tract infections is also discussed in the section on canine infectious tracheobronchitis in this chapter (p. 285) and in the section on bacterial pneumonia in Chapter 22.

Tracheobronchomalacia is discussed on p. 297, and pulmonary hypertension is discussed in Chapter 22.

#### **Prognosis**

Canine chronic bronchitis cannot be completely cured. The prognosis for the control of signs and a satisfactory quality of life in animals is good if the owners are conscientious about performing the medical management aspects of care, are willing to adjust treatment over time, and treat secondary problems as they occur.

## **FELINE BRONCHITIS (IDIOPATHIC)**

#### Etiology

Cats with respiratory disease of many etiologies present with signs of bronchitis or asthma. Cat airways are much more reactive, prone to bronchoconstriction, than dogs. The common presenting signs of bronchitis (i.e., cough, wheezing, and/or respiratory distress) can occur in cats with diseases as varied as lung parasites, heartworm disease, allergic bronchitis, bacterial or viral bronchitis, toxoplasmosis, idiopathic pulmonary fibrosis, carcinoma, and aspiration pneumonia (Table 21-2). Veterinarians often assume that cats with presenting signs of bronchitis or asthma have idiopathic disease because in most cats an underlying etiology cannot be found. However, as with canine chronic bronchitis, a diagnosis of idiopathic feline bronchitis can be made only by ruling out other active disease. Care should be taken when using the terms feline bronchitis or feline asthma to distinguish between a presentation consistent with bronchitis in a broad sense and a clinical diagnosis of idiopathic disease. Cats with idiopathic bronchitis often have some degree of airway eosinophilia, typical of an allergic reaction. This author prefers to reserve the diagnosis of allergic bronchitis to patients who respond dramatically to the elimination of a suspected allergen (see p. 299).

A wide variety of pathologic processes can affect individual cats with idiopathic bronchitis. Clinically, the range in the severity of signs and the response to therapy shows this diversity. Different combinations of factors that result in small airway obstruction, a consistent feature of feline bronchial disease, are present in each animal (Box 21-3). Some of these factors are reversible (e.g., bronchospasm, inflammation), and some are permanent (e.g., fibrosis, emphysema). The classification proposed by Moise et al. (1989), which was formulated on the basis of similar pathologic processes that occur in people, is recommended as a way to better define bronchial disease in individual cats for the purpose of treatment recommendations and prognostication (Box 21-4). A cat can also have more than one type of bronchitis. Although it is not always possible to absolutely determine the type or types of bronchial disease present without sophisticated pulmonary function testing, routine clinical data (i.e., history and physical examination findings, thoracic radiographs, analysis of airway specimens, progression of signs) can be used to classify the disease in most cats.



Differential Diagnoses (Etiologic) for Cats with Presenting Signs of Bronchitis

#### **DIAGNOSIS**

## DISTINGUISHING FEATURES COMPARED WITH IDIOPATHIC FELINE BRONCHITIS

Allergic bronchitis

Pulmonary parasites (Aelurostrongylus abstrusus; Capillaria aerophila; Paragonimus kellicotti) Heartworm disease

Bacterial bronchitis

Mycoplasmal bronchitis

Idiopathic pulmonary fibrosis

Carcinoma

Toxoplasmosis

Aspiration pneumonia

Idiopathic feline bronchitis

BAL, bronchoalveolar lavage.

Dramatic clinical response to elimination of suspected allergen(s) from environment or diet.

Thoracic radiographs may have a nodular pattern; Larvae (*Aelurostongylus*) or eggs identified in tracheal wash or BAL fluid or in the feces. See Chapter 20 for appropriate procedures for fecal testing.

Pulmonary artery enlargement may be present on thoracic radiographs; positive heartworm antigen test or identification of adult worm(s) on echocardiography (see Chapter 10).

Intracellular bacteria in tracheal wash or BAL fluid and significant growth on culture (see Chapter 20).

Growth of Mycoplasma on specific culture of tracheal wash or BAL fluid (presence may indicate primary infection, secondary infection, or be incidental).

Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis; diagnosis requires lung biopsy (see Chapter 22).

Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis. Cytologic or histologic identification of malignant cells in tracheal wash or BAL fluid, lung aspirates, or lung biopsy. Histologic confirmation is ideal.

Systemic signs usually present (fever, anorexia, depression). Radiographs may show more severe infiltrates than expected in cats with idiopathic bronchitis, possibly with a nodular pattern. Diagnosis is confirmed by identification of organisms (tachyzoites) in tracheal wash or BAL fluid. Rising serum antibody titers or elevated IgM concentrations are supportive of the diagnosis (see Chapter 99).

Unusual in cats. History supportive of a predisposing event or condition. Radiographs typically show an alveolar pattern, worse in the dependent (cranial and middle) lung lobes. Neutrophilic inflammation, usually with bacteria, in tracheal wash fluid.

Elimination of other diseases from the differential diagnoses.



BOX 21-3

Factors that Can Contribute to Small Airway Obstruction in Cats with Bronchial Disease

Bronchoconstriction
Bronchial smooth muscle hypertrophy
Increased mucus production
Decreased mucus clearance
Inflammatory exudate in airway lumens
Inflammatory infiltrate in airway walls
Epithelial hyperplasia
Glandular hypertrophy
Fibrosis
Emphysema



BOX 21-4

Classification of Feline Bronchial Disease

#### **Bronchial Asthma**

Predominant feature: reversible airway obstruction primarily resulting from bronchoconstriction

Other common features: hypertrophy of smooth muscle, increased mucus production, eosinophilic inflammation

#### **Acute Bronchitis**

Predominant feature: reversible airway inflammation of short duration (<1-3 months)

Other common features: increased mucus production, neutrophilic or macrophagic inflammation

#### **Chronic Bronchitis**

Predominant feature: chronic airway inflammation (>2-3 months) resulting in irreversible damage (e.g., fibrosis)
Other common features: increased mucus production; neutrophilic, eosinophilic, or mixed inflammation; isolation of bacteria or Mycoplasma organisms causing infection or as nonpathogenic inhabitants; concurrent bronchial asthma

#### Emphysema

Predominant feature: destruction of bronchiolar and alveolar walls resulting in enlarged peripheral air spaces Other common features: cavitary lesions (bullae); result of or concurrent with chronic bronchitis

Adapted from Moise NS et al: Bronchopulmonary disease. In Sherding RG, editor: *The cat: diseases and clinical management,* New York, 1989, Churchill Livingstone.

## **Clinical Features**

Idiopathic bronchitis can develop in cats of any age, although it most commonly develops in young adult and middle-aged animals. The major clinical feature is cough or episodic respiratory distress or both. The owners may report audible wheezing during an episode. The signs are often slowly progressive. Weight loss, anorexia, depression, or other systemic

signs are not present. If systemic signs are identified, another diagnosis should be aggressively pursued.

Owners should be carefully questioned regarding an association with exposure to potential allergens or irritants. Irritants in the environment can cause worsening of signs of bronchitis regardless of the underlying etiology. Environmental considerations include exposure to new litter (usually perfumed), cigarette or fireplace smoke, carpet cleaners, and household items containing perfumes such as deodorant or hair spray. Clients should also be questioned about whether there has been any recent remodeling or any other change in the cat's environment. Seasonal exacerbations are suggestive of potential allergen exposure.

Physical examination abnormalities result from small airway obstruction. Cats that are in distress show tachypnea. Typically the increased respiratory efforts are more pronounced during expiration, and auscultation reveals expiratory wheezes. Crackles are occasionally present. In some patients in distress, hyperinflation of the lungs due to air trapping may result in increased inspiratory efforts and decreased lung sounds. Physical examination findings may be unremarkable between episodes.

## Diagnosis

A diagnosis of idiopathic feline bronchitis is made on the basis of typical historical, physical examination, and thoracic radiographic findings and the elimination of other possible differential diagnoses (see Table 21-2). A thorough search for other diagnoses is highly recommended, even though a specific diagnosis is not commonly found, because identifying an etiology for the clinical signs may allow for specific treatment and even cure of an individual cat. Factors to consider when developing a diagnostic plan include the clinical condition of the cat and the client's tolerance for expense and risk. Cats that are in respiratory distress or are otherwise in critical condition should not undergo any stressful testing until their condition has stabilized. Sufficiently stable cats that have any indication of a diagnosis other than idiopathic disease on the basis of presenting signs and thoracic radiographs or any subsequent test results require a thorough evaluation. Certain tests are completely safe, such as fecal testing for pulmonary parasites, and their inclusion in the diagnostic plan is largely based on financial considerations. In most cats with signs of bronchitis, collection of tracheal wash fluid for cytology and culture and tests for pulmonary parasitism and heartworm disease are recommended.

A CBC is often performed as a routine screening test. Cats with idiopathic bronchitis are often thought to have peripheral eosinophilia. However, this finding is neither specific nor sensitive and cannot be used to rule out or definitively diagnose feline bronchitis.

Thoracic radiographs from cats with bronchitis generally show a bronchial pattern (see Fig. 20-3). Increased reticular interstitial markings and patchy alveolar opacities may also be present. The lungs may be seen to be overinflated as a result of the trapping of air, and occasionally collapse (i.e., atelectasis) of the right middle lung lobe is seen (see Fig.

20-9). However, because clinical signs can precede radiographic changes and because radiographs cannot detect mild airway changes, thoracic radiographs may be normal in cats with bronchitis. Radiographs are also scrutinized for signs of specific diseases (see Table 21-2).

The tracheal wash or BAL fluid cytologic findings are generally representative of the airway inflammation and consist of increased numbers of inflammatory cells and an increased amount of mucus. Inflammation can be eosinophilic, neutrophilic, or mixed. Although not a specific finding, eosinophilic inflammation is suggestive of a hypersensitivity response to allergens or parasites. Neutrophils should be examined for signs of the degeneration suggestive of bacterial infection. Slides should be carefully scrutinized for the presence of organisms, particularly bacteria and parasitic larvae or ova. Fluid should be cultured for bacteria, although it is important to note that the growth of organisms may or may not indicate the existence of true infection (see Chapter 20). Cultures for *Mycoplasma* spp. may also be helpful.

Testing for heartworm disease is described in Chapter 10. Multiple fecal examinations using special concentrating techniques are performed to identify pulmonary parasites, particularly in young cats and cats with airway eosinophilia (see Chapter 20). Other tests may be indicated for individual cats.

#### **Treatment**

### **EMERGENCY STABILIZATION**

The condition of cats in acute respiratory distress should be stabilized before diagnostic tests are performed. Successful treatment includes administration of a bronchodilator, rapid-acting glucocorticoids, and oxygen supplementation. Terbutaline can be administered subcutaneously, a route that avoids additional patient stress (see Box 21-2). Prednisolone sodium succinate is the recommended glucocorticoid for a life-threatening crisis (up to 10 mg/kg, administered intravenously). If intravenous administration is too stressful, the drug can be given intramuscularly. Alternatively, dexamethasone sodium phosphate (up to 2 mg/kg, administered intravenously) can be given. After the drugs are administered, the cat is placed in a cool, stress-free, oxygen-enriched environment. If additional bronchodilation is desired, albuterol can be administered by nebulization or metered-dose inhaler (MDI). Administration of drugs by MDI is described later in this section. (See Chapter 26 for further discussion of cats with respiratory distress.)

### **ENVIRONMENT**

The potential influence of the environment on clinical signs should be investigated. Allergic bronchitis is diagnosed through the elimination of potential allergens from the environment (see the section on allergic bronchitis). However, even cats with idiopathic bronchitis can benefit from improvement in indoor air quality through the reduction of irritants or unidentified allergens. Potential sources of allergens or irritants are determined through careful

owner questioning as described in the section on clinical features. Smoke can often aggravate signs because of its local irritating effects. The effect of litter perfumes can be evaluated by replacing the litter with sandbox sand or plain clay litter. Indoor cats may show improvement in response to measures taken to decrease the level of dusts, molds, and mildew in the home. Such measures include carpet, furniture, and drapery cleaning; cleaning of the furnace and the frequent replacement of air filters; and the use of an air cleaner. The American Lung Association has a useful website with nonproprietary recommendations for improving indoor air quality (www.lungusa.org). Any beneficial response to an environmental change is usually seen within 1 to 2 weeks.

#### **GLUCOCORTICOIDS**

Therapy with glucocorticoids, with or without bronchodilators, is necessary for most cats with idiopathic bronchitis. Results can be dramatic. However, drug therapy can interfere with environmental testing; therefore the ability of the animal to tolerate a delay in the start of drug therapy must be assessed on an animal-by-animal basis. Glucocorticoids can relieve the clinical signs in most cats and may protect the airways from the detrimental effects of chronic inflammation. Short-acting products such as prednisolone are recommended because the dose can be tapered to the lowest effective amount. Anecdotal experience and a preliminary study suggest that prednisolone may be more effective in cats than prednisone (Graham-Mize et al., 2004). A dose of 0.5 to 1 mg/kg is administered every 12 hours initially, with the dose doubled if signs are not controlled within 1 week. Once the signs are well controlled, the dose is tapered. A reasonable goal is to administer 0.5 mg/kg or less every other day. Outdoor cats that cannot be treated frequently can be administered depot steroid products, such as methylprednisolone acetate (10 mg/cat intramuscularly may be effective for up to 4 weeks).

Glucocorticoids, such as fluticasone propionate (Flovent, GlaxoSmithKline), can also be administered locally to the airways by MDI, as is routine for treating asthma in people. The advantages are minimal systemic side effects and relative ease of administration in some cats compared with pilling. To date, however, it is still not known how much drug is deposited in the lower airways, how much remains in the oral and nasal cavities, and how much is absorbed systemically in cats. Theoretical concerns about the oronasal deposition of the potent glucocorticoid in cats, compared with people, include the high incidence of periodontal disease and latent herpesvirus infections and the inability to effectively rinse the mouth with water after use. Local dermatitis because of mites, dermatophytes, or bacteria can occur. However, some veterinarians have been using glucocorticoid MDIs to treat idiopathic feline bronchitis for many years without frequent, obvious adverse effects.

This author prefers to obtain a clinical remission of signs using orally administered drug first, except in cats with relative contraindications for systemic glucocorticoid therapy, such as diabetes mellitus. Cats that require a relatively low

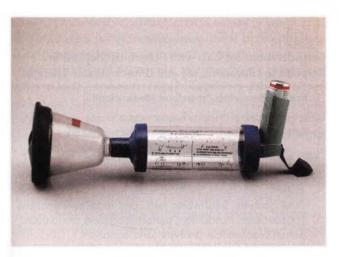


FIG 21-4
Apparatus for administering drugs by metered dose inhaler (MDI) to cats consisting of an anesthetic mask, spacer (OptiChamber, Respironics, Inc., Pittsburgh, Pa.), and MDI (Ventolin, GlaxoSmithKline, Research Triangle Park, N.C.).

dose of oral glucocorticoids to control clinical signs, have no noticeable adverse effects, and can be pilled without difficulty are often well maintained with oral therapy. Otherwise, once signs are in remission, treatment by MDI is initiated and the dosage of oral prednisolone gradually reduced.

A spacer must be used for effectively administering drugs by MDI to cats, and the airflow generated by the cat must be sufficient to activate the spacer valve. Padrid (2000) has found the OptiChamber (Respironics, Inc) to be effective (Fig. 21-4). A small anesthetic mask, with rubber diaphragm, is attached to the spacer. Widening of the adapter of the anesthetic mask that is inserted into the spacer is necessary to create a snug fit. This is achieved by wrapping adhesive tape around the adapter. Alternatively, a mask with spacer specifically designed for use in cats is available (Aerokat, Trudell Medical International). The cat is allowed to rest comfortably on a table or in the client's lap. The client places his or her arms on either side of the cat or gently steadies the cat's neck and head to provide restraint (Fig. 21-5). The MDI, attached to the spacer, is actuated (i.e., pressed) twice. The mask is placed immediately on the cat's face, covering the mouth and nose completely, and is held in place while the cat takes 7 to 10 breaths, inhaling the drug into its airways.

The following treatment schedule has been recommended (Padrid, 2000): Cats with mild daily symptoms should receive 220 Lg of fluticasone propionate by MDI twice daily and albuterol by MDI as needed. The maximal effect of fluticasone is not expected until 7 to 10 days of treatment. Cats with moderate daily symptoms should receive treatments with MDI as described for mild symptoms; in addition, prednisolone is administered orally for 10 days (1 mg/kg every 12 hours for 5 days, then every 24 hours for 5 days). For cats with severe symptoms, dexamethasone is administered once (2 mg/kg, intravenously), albuterol is adminis-



FIG 21-5
Administering drugs by metered-dose inhaler (MDI) to a cat.
The mask and chamber apparatus is the Aerokat (Trudell Medical International, London, Ontario, Canada).

tered by MDI every 30 minutes for up to 4 hours, and oxygen is administered. Once stabilized, these cats are prescribed 220  $\mu$ g of fluticasone propionate by MDI every 12 hours and albuterol by MDI every 6 hours as needed. Oral prednisolone is administered as needed.

#### **BRONCHODILATORS**

Cats that require relatively large amounts of glucocorticoids to control clinical signs, react unfavorably to glucocorticoid therapy, or suffer from periodic exacerbations of signs can benefit from bronchodilator therapy. Recommended doses of these drugs are listed in Box 21-2.

This author prefers to use theophylline because it is effective and inexpensive and can be given to cats once daily; moreover, the plasma concentrations can be easily measured for the monitoring of difficult cases. Additional properties of theophylline, potential drug interactions, and adverse effects are described in the section on canine chronic bronchitis (p. 290).

The pharmacokinetics of theophylline products are different in cats compared with dogs, resulting in different dosages (see Box 21-2). Variability in sustained plasma concentrations in both species has been found for different longacting theophylline products. Dosage recommendations are currently available for a generic product from a specific manufacturer (Box 21-2). However, the individual metabolism of all of the methylxanthines is variable. If beneficial effects are not seen, the patient is predisposed to adverse effects, or adverse effects occur, plasma theophylline concentrations should be measured. Therapeutic peak concentrations, based on data from human subjects, are 5 to 20 g/ml. Plasma for the determination of these concentrations should be collected 12 hours after the evening dosing of the longacting products and 2 hours after short-acting products. Measurement of concentrations immediately before the next scheduled dose might provide useful information concerning duration of therapeutic concentrations.

Sympathomimetic drugs can also be effective bronchodilators. Terbutaline is selective for  $\beta_2$ -adrenergic receptors, lessening its cardiac effects. Potential adverse effects include nervousness, tremors, hypotension, and tachycardia. It can be administered subcutaneously for the treatment of respiratory emergencies; it can also be administered orally. Note that the recommended oral dose for cats (one eighth to one fourth of a 2.5-mg tablet; see Box 21-2) is lower than the commonly cited dose of 1.25 mg/cat. The subcutaneous dose is lower still: 0.01 mg/kg, repeated once in 5 to 10 minutes if necessary.

Bronchodilators can be administered to cats by MDI for the immediate treatment of acute respiratory distress (asthma attack). Cats with idiopathic bronchitis are routinely prescribed an albuterol MDI, spacer, and mask (see the section on glucocorticoids for details) to be kept at home for emergencies.

#### OTHER POTENTIAL TREATMENTS

A therapeutic trial with an antibiotic effective against *Mycoplasma* is considered because of the difficulty in documenting infection with this organism. Either doxycycline (5 to 10 mg/kg q12h) or chloramphenicol (10 to 15 mg/kg q12h) is administered for 14 days. For cats that are difficult to medicate, azithromycin (5 to 10 mg/kg q24h for 3 days, then q72h) can be tried. Remember that administration of doxycycline should always be followed with a bolus of water to minimize the incidence of esophageal stricture.

Antihistamines are not recommended for treating feline bronchitis because histamine in some cats produces bronchodilation. However, work done by Padrid et al. (1995) has shown that the serotonin antagonist, cyproheptadine, has a bronchodilatory effect *in vitro*. A dose of 2 mg/cat orally every 12 hours can be tried in cats with signs that cannot be controlled with routine bronchodilator and glucocorticoid therapy. This treatment is not consistently effective.

Much interest has been shown among clients and veterinarians in the use of oral leukotriene inhibitors in cats (e.g., Accolate, Singulair, and Zyflo). However, the clinician should be aware that in people, leukotriene inhibitors are *less* effective in the management of asthma than glucocorticoids, and they are not used in the emergency management of the disease or for refractory cases. Their advantage for people lies in decreased side effects, compared with glucocorticoids, and ease of administration. To date, toxicity studies have not been performed on these drugs in cats. Furthermore, several preliminary studies suggest that leukotriene inhibition in cats would not be expected to have efficacy comparable to that in people. Therefore their routine use in cats is not currently advocated. Further investigation into their potential role in treating feline bronchitis is certainly indicated.

## FAILURE TO RESPOND

The clinician should ask himself or herself the questions listed in Box 21-5 if cats fail to respond to glucocorticoid and bronchodilator therapy or if exacerbation of signs occurs during chronic treatment.



BOX 21-5

Considerations for Cats with Bronchitis that Fail to Respond to Glucocorticoid and Bronchodilator Therapy

#### Is the Cat Receiving Prescribed Medication?

Measure plasma theophylline concentrations. Initiate trial therapy with repositol glucocorticoids.

## Was an Underlying Disease Missed on Initial Evaluation?

Repeat diagnostic evaluation, including complete history for potential allergens, thoracic radiographs, tracheal wash fluid analysis, heartworm tests, and fecal examinations for parasites. In addition, perform complete blood count, serum biochemical analysis, and urinalysis.

Initiate trial therapy with anti-Mycoplasma drug.
Initiate trial environmental manipulations to minimize potential allergen and irritant exposure.

#### Has a Complicating Disease Developed?

Repeat diagnostic evaluation as described in the preceding sections.

## **Prognosis**

The prognosis for the control of clinical signs of idiopathic feline bronchitis is good for most cats, particularly if extensive permanent damage has not yet occurred. Complete cure is unlikely, and most cats require continued medication. Cats that have severe, acute asthmatic attacks are at risk for sudden death. Cats with persistent, untreated airway inflammation can develop the permanent changes of chronic bronchitis and emphysema.

## COLLAPSING TRACHEA AND TRACHEOBRONCHOMALACIA

## Etiology

The normal trachea is seen to be circular on cross section (see Fig. 21-8, *B*, and Fig. 20-27, *A*). An open lumen is maintained during all phases of quiet respiration by the cartilaginous tracheal rings, which are connected by fibroelastic annular ligaments to maintain flexibility, thereby allowing movement of the neck without compromising the airway. The cartilaginous rings are incomplete dorsally. The dorsal tracheal membrane, consisting of the longitudinal tracheal muscle and connective tissue, completes the rings. The term *tracheal collapse* refers to the narrowing of the tracheal lumen resulting from weakening of the cartilaginous rings, a redundancy of the dorsal tracheal membrane, or both. The condition can affect the extrathoracic trachea, the intrathoracic trachea, or both.

A credible theory of the pathogenesis of tracheal collapse is that certain dogs are predisposed to collapse because of inherent abnormalities in their cartilage but are initially asymptomatic. An exacerbating problem develops that

results in increased respiratory efforts, airway inflammation, and/or cough. Changes in intrathoracic and airway pressures during increased respiratory efforts or cough likely contribute to narrowing of the trachea, and the chronic presence of inflammatory mediators (e.g., collagenases and proteases) within the trachea likely further weaken its structure. Any narrowing of the trachea results in greatly increased resistance to air flow and local turbulence because the resistance to airflow is proportional to the reciprocal of the radius of the lumen to the fourth power. This increased resistance may further contribute to a cycle of increased respiratory efforts, cough, and inflammation. In addition, as described for canine chronic bronchitis, a continuing cycle of inflammation is also plausible as a result of mucosal damage. Mucus hypersecretion and airway obstruction impair normal mucociliary clearance, and inflammatory mediators amplify the response to irritants and organisms.

Clinically, tracheal collapse often occurs in conjunction with canine chronic bronchitis. In dogs with chronic bronchitis, the intrathoracic trachea is most often affected. Dogs with chronic bronchitis may initially demonstrate collapse of their major (mainstem and/or lobar) bronchi. The lumen of these airways is normally maintained by rafts of cartilage within their walls, rather than rings. Chronic exposure to inflammatory mediators presumably plays a role in the resultant loss of normal airway structure. In addition, obstruction of smaller airways because of excess mucus and mucosal alterations may decrease the intraluminal airway pressures in the larger airways during expiration and contribute to airway collapse. The general term for weakening of the normal tracheal and bronchial structure is *tracheobronchomalacia*.

As a result of intrathoracic and airway pressures, the extrathoracic trachea tends to collapse during inspiration. The intrathoracic trachea and mainstem and lobar bronchi tend to collapse during expiration.

#### **Clinical Features**

Tracheal collapse is common in middle-aged toy and miniature dogs, although it also can occur early in life and in large-breed dogs. Signs may occur acutely but then slowly progress over months to years. The primary clinical feature in most dogs is a nonproductive cough, described as a "goose honk." The cough is worse during excitement or exercise or when the collar exerts pressure on the neck. Eventually (usually after years of chronic cough), respiratory distress caused by obstruction to airflow may be brought on by excitement, exercise, or overheating. Systemic signs such as weight loss, anorexia, and depression are not expected. Occasionally, dogs are presented primarily for signs of upper airway obstruction without cough, also exacerbated during excitement, exercise, or hot weather. Stertorous sounds may be heard during periods of increased respiratory efforts. Such signs are usually the result of extrathoracic tracheal collapse. Tracheal collapse is rare in cats, and most often it occurs secondary to a tracheal obstruction such as a tumor or traumatic injury.

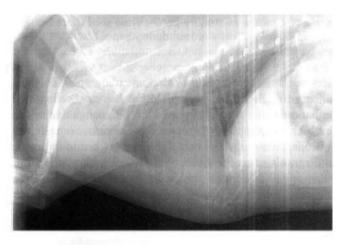
On physical examination a cough can usually be elicited by palpation of the trachea. An end-expiratory snap or click may be heard during auscultation if intrathoracic collapse is present. In advanced cases or after exercise, increased inspiratory effort may be observed in dogs with extrathoracic collapse and increased expiratory effort observed in those with intrathoracic collapse, often accompanied by audible sounds.

History and physical examination should also emphasize a search for exacerbating or complicating disease. The frequent association with canine chronic bronchitis has been mentioned. Other possibilities include cardiac disease causing left atrial enlargement with bronchial compression or pulmonary edema; airway inflammation caused by bacterial infection, allergic bronchitis, exposure to smoke (e.g., from cigarettes, fireplaces), or recent intubation; upper airway obstruction caused by elongated soft palate, stenotic nares, or laryngeal paralysis; and systemic disorders such as obesity or hyperadrenocorticism.

## Diagnosis

Collapsing trachea is most often diagnosed on the basis of clinical signs and the findings from cervical and thoracic radiography. Radiographs of the neck to evaluate the size of the lumen of the extrathoracic trachea are taken during inspiration (Fig. 21-6), when narrowing caused by tracheal collapse is more evident because of negative airway pressure. Conversely, the size of the lumen of the intrathoracic trachea is evaluated on thoracic radiographs taken during expiration, when increased intrathoracic pressures make collapse more apparent (Fig. 21-7). Radiographs of the thorax should also be taken during inspiration to detect concurrent bronchial or parenchymal abnormalities. (See Chapter 20 for further discussion of radiography.)

Fluoroscopic evaluation provides a "motion picture" view of large airway dynamics, making changes in luminal diam-



Lateral radiograph of the thorax and neck of a dog with collapsing trachea taken during inspiration. The extrathoracic airway stripe is severely narrowed cranial to the thoracic inlet.

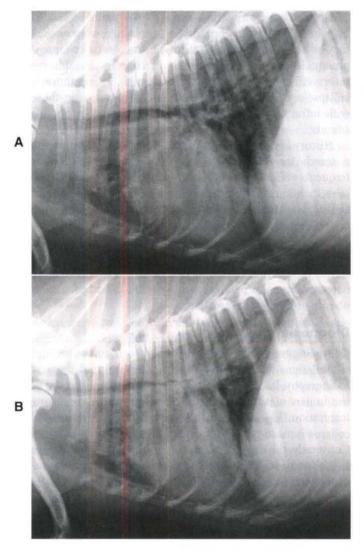


FIG 21-7
Lateral radiographs of a dog with tracheobronchomalacia.
During inspiration (A) the trachea and mainstem bronchi are nearly normal. During expiration (B) the intrathoracic trachea and mainstem bronchi are markedly narrowed.
Evaluation of the pulmonary parenchyma should not be attempted using films exposed during expiration.

eter easier to identify than by routine radiography. The sensitivity of fluoroscopy in detecting airway collapse is enhanced if the patient can be induced to cough during the evaluation by applying pressure to the trachea. Some degree of collapse is probably normal during cough, and in people a diagnosis of tracheobronchomalacia is generally made if the luminal diameter decreases by greater than 50% during forced exhalation.

Bronchoscopy is also useful in the diagnosis of airway collapse (Fig. 21-8; see also Fig. 21-3). The bronchi of smaller dogs may be difficult to evaluate by radiography or fluoroscopy but are easily examined bronchoscopically. Bronchoscopy and the collection of airway specimens (such as by BAL) is useful for identifying exacerbating or concurrent conditions.

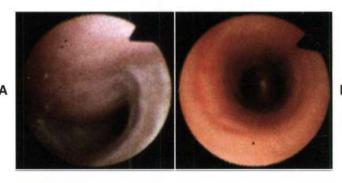


FIG 21-8
Bronchoscopic images from a dog with tracheal collapse
(A). The dorsal tracheal membrane is much wider than that of a normal dog (B). The airway lumen is greatly compromised.

Bronchoscopy is performed with the patient under general anesthesia, which interferes with the ability to induce cough. However, allowing the patient to reach a light plane of anesthesia combined with the manipulation of the airways will often cause more forceful respirations that increase the likelihood of identifying airway collapse.

Additional tests are performed to identify exacerbating or concurrent conditions. Tracheal wash fluid is analyzed by cytology and culture if bronchoscopy and BAL are not done. Other considerations include an upper airway examination, cardiac evaluation, and screening for systemic disease.

#### **Treatment**

Medical therapy is adequate treatment for most animals. In a study of 100 dogs by White et al. (1994), medical therapy resulted in resolution of signs for at least 1 year in 71% of cases. Dogs that are overweight are placed on a weight-reducing diet. Harnesses should be used instead of collars, and owners should be counseled to keep their dogs from becoming overheated (e.g., they should not be left in a car). Excessive excitement should also be avoided. Sedatives such as phenobarbital are prescribed for some animals, and these can be administered before known stressful events.

Cough suppressants are used to control signs and disrupt the potential cycle of perpetuating cough (see Table 21-1). The dose and frequency of administration of cough suppressants are adjusted as needed. Initially, high, frequent dosing may be needed to break the cycle of coughing. Subsequently, it is often possible to decrease frequency of administration and dose. Bronchodilators may be beneficial in dogs with signs of chronic bronchitis (see p. 290). Antiinflammatory doses of glucocorticoids can be given for a short period during exacerbation of signs (prednisone, 0.5 to 1 mg/kg q12h for 3 to 5 days, then tapered and discontinued over 3 to 4 weeks). Long-term use is not recommended because of potential detrimental side effects such as obesity, but this is often necessary to control signs in patients with chronic bronchitis. Dogs with signs referable to mitral insufficiency are managed for this disease (see Chapter 8). Dogs with abnormalities causing upper airway obstruction are treated with corrective surgical procedures.

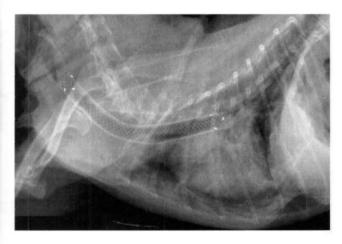


FIG 21-9
Lateral radiograph of the dog with tracheal collapse shown in Fig. 21-6 after placement of an intraluminal stent. The stent is has a meshlike structure and extends nearly the entire length of the trachea.

Antibiotics are not indicated for the routine management of a collapsing trachea. Dogs in which tracheal wash or BAL fluid analysis has revealed evidence of infection should be treated with appropriate antibiotics (selected on the basis of the results of sensitivity testing). Because most antibiotics do not reach high concentrations in the airways, relatively high doses of antibiotics should be administered for several weeks, as described for canine chronic bronchitis (p. 291). Any other potential related problems identified during the diagnostic evaluation are addressed.

Management of dogs in acute distress with signs of either extrathoracic airway obstruction or intrathoracic large airway obstruction is discussed in Chapter 26.

Surgical treatment of a collapsing trachea should be considered for animals that are no longer responsive to medical management, usually because of respiratory difficulty. The introduction of intraluminal stents has greatly reduced the morbidity and improved the success of surgical intervention. The most commonly used stents are self-expanding and made of nickel-titanium alloys (Fig. 21-9). In experienced hands, these stents are simple to place during a short period of anesthesia using fluoroscopic or bronchoscopic guidance. There is minimal morbidity associated with stent placement, and response is immediate and often dramatic. However, clinical signs (particularly cough) may not completely resolve, collapse of airways beyond the trachea and concurrent conditions are not directly addressed (often resulting in the continued need for medical management), and complications such as granuloma formation and stent fracture can occur. Results from stent placement are sufficiently encouraging that motivated clients with a dog that is failing medical management of tracheal collapse should be referred to someone experienced in stent placement for further consideration of this option.

#### **Prognosis**

In most dogs clinical signs can be controlled with conscientiously performed medical management, with diagnostic

evaluations performed during episodes of persistent exacerbations of signs. Animals in which severe signs develop despite appropriate medical care have a guarded prognosis, and motivated clients should be referred for possible stent placement.

#### **ALLERGIC BRONCHITIS**

Allergic bronchitis is a hypersensitivity response of the airways to an allergen or allergens. The offending allergens are presumably inhaled, although food allergens could also be involved. A definitive diagnosis requires identification of allergen(s) and resolution of signs after elimination of the allergen(s). Large controlled studies describing allergic bronchitis in dogs or cats are lacking. A study by Prost (2004) presented as an abstract found that 15 of 20 cats had positive intradermal skin tests to aeroallergens. For cats that reacted to storage mites or cockroach antigen, discontinuation of any dry food was recommended (i.e., only canned food was provided). Remission of signs occurred in 3 cats with only this treatment. Immunotherapy (desensitization) appeared to reduce or eliminate signs in some of the other cats. As a preliminary study, other treatments were also given to the study cats, and a control population was not described.

It is likely that some patients with allergic bronchitis are misdiagnosed because of difficulty in identifying specific allergens. In dogs long-standing allergic bronchitis may result in the permanent changes recognized as canine chronic bronchitis. In cats failure to identify specific allergen(s) results in a diagnosis of idiopathic feline bronchitis.

Allergic bronchitis in dogs may result in acute or chronic cough. Rarely, respiratory distress and wheezing occur. The physical examination and radiographic findings reflect the presence of bronchial disease, as described in the section on canine chronic bronchitis. Eosinophilic inflammation is expected in tracheal wash or BAL fluid. Heartworm tests and fecal examinations for pulmonary parasites are performed to eliminate parasitism as the cause of the eosinophilic inflammation. In dogs younger than than 2 years of age, bronchoscopic evaluation for *Oslerus osleri* also should be considered (see the following section). Allergic bronchitis in cats has the same presentation and results of diagnostic testing as described for idiopathic feline bronchitis, with eosinophilia expected in airway specimens.

Management of allergic bronchitis is initially focused on identifying and eliminating potential allergens from the environment (see the section on feline bronchitis). Diet trials with novel protein and carbohydrate sources also can be considered. According to the preliminary study previously described, a change in diet to canned food may be beneficial in some cases. Such experimentation with environment and diet is possible only in patients with clinical signs that are sufficiently mild to delay the administration of glucocorticoids and bronchodilators, as described in the sections on canine chronic bronchitis and feline bronchitis (idiopathic). Elimination trials can still be pursued once clinical signs are

controlled with medications, but confirmation of a beneficial effect will require discontinuation of the medication and, for a definitive diagnosis to be made, reintroduction of the allergen. The latter may not be necessary or practical in all cases.

#### **OSLERUS OSLERI**

#### **Etiology**

Oslerus osleri is an uncommon parasite of young dogs, usually those younger than 2 years of age. The adult worms live at the carina and mainstem bronchi and cause a local, nodular inflammatory reaction with fibrosis. First-stage larvae are coughed up and swallowed. The main cause of infection in dogs appears to be through intimate contact with their dam as puppies.

#### **Clinical Features**

Young affected dogs have an acute, loud, nonproductive cough and occasionally wheezing. The dogs appear otherwise healthy, making the initial presentation indistinguishable from that of canine infectious tracheobronchitis. However, the cough persists, and eventually airway obstruction occurs as a result of the formation of reactive nodules.

#### **Diagnosis**

Nodules at the carina occasionally can be recognized radiographically. Cytologic examination of tracheal wash fluid in some dogs shows the characteristic ova or larvae, providing the basis for a definitive diagnosis (see Table 20-1). Rarely, larvae are found in fecal specimens using zinc sulfate (s.g. 1.18) flotation (preferred) or the Baermann technique (see Box 20-8).

The most sensitive diagnostic method is bronchoscopy, which enables the nodules to be readily seen (Fig. 21-10). Brushings of the nodules are obtained and immediately evaluated cytologically to detect the larvae. Material can be examined directly in saline solution or stained with new methylene blue. If a definitive diagnosis is not obtained from analysis of the brushings, biopsy specimens are obtained.

#### **Treatment**

Treatment with ivermectin (400 µ g/kg orally or subcutaneously) is recommended. The same dose is administered again every 3 weeks for four treatments. This treatment has not been extensively investigated, however, and is not an approved use of this drug. It cannot be administered to Collies or related breeds. An alternative treatment is fenbendazole (50 mg/kg q24h for 7 to 14 days).

#### **Prognosis**

The prognosis for dogs treated with ivermectin is good; the drug appears to be successful in eliminating infection in the limited number of dogs that have been treated. Follow-up of individual patients is indicated to ensure successful elimination.

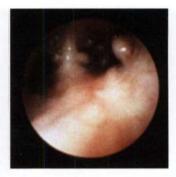


FIG 21-10
Bronchoscopic view of multiple nodules at the carina of a dog infected with Oslerus osleri.

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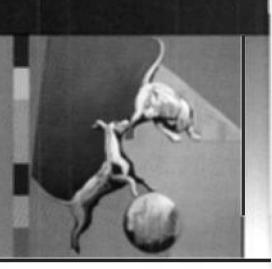
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## CHAPTER

# Disorders of the Pulmonary Parenchyma and Vasculature



#### CHAPTER OUTLINE

VIRAL PNEUMONIAS

Canine Influenza

Other Viral Pneumonias

BACTERIAL PNEUMONIA

**TOXOPLASMOSIS** 

FUNGAL PNEUMONIA

PULMONARY PARASITES

Capillaria (Eucoleus) aerophila

Paragonimus kellicotti

Aelurostrongylus abstrusus

Crenosoma vulpis

ASPIRATION PNEUMONIA

EOSINOPHILIC LUNG DISEASE (PULMONARY

INFILTRATES WITH EOSINOPHILS AND

EOSINOPHILIC PULMONARY GRANULOMATOSIS)

IDIOPATHIC INTERSTITIAL PNEUMONIAS

Idiopathic Pulmonary Fibrosis

PULMONARY NEOPLASIA

PULMONARY HYPERTENSION

PULMONARY THROMBOEMBOLISM

PULMONARY EDEMA

#### VIRAL PNEUMONIAS

#### **CANINE INFLUENZA**

#### Etiology

The canine influenza virus appears to be a recent adaptation from an equine influenza virus (Crawford et al., 2005). Serologic evidence has been found to support its existence among racing greyhounds since 1999 (Anderson et al., 2007). Therefore most dogs are susceptible to infection regardless of age, and spread among dogs in contact with one another, especially those housed together, is rapid. The virus is transmitted through respiratory secretions that are aerosolized or contaminate objects, including hands, clothing, bowls, and

kennels. Dogs are thought to shed the virus for up to 10 days after the first appearance of clinical signs, and shedding can also occur from the nearly 20% of infected dogs that never develop clinical signs (Crawford, 2005).

#### **Clinical Features**

The disease is most frequently identified during outbreaks among dogs in group housing, such as race tracks and animal shelters. Individual pets often have a recent history (usually in the previous week) of exposure to other dogs. Clinical signs of canine influenza in most dogs are similar to those of infectious tracheobronchitis (see p. 285). This mild form of the disease causes a cough that can be harsh and loud, as typically heard with infectious tracheobronchitis, but that is more often soft and moist. Some dogs may have concurrent mucopurulent nasal discharge, a less common finding in infectious tracheobronchitis.

Dogs with the severe form of disease develop overt pneumonia, peracutely or after having acough for up to 10 days (Crawford, 2005). Secondary bacteria infection is common. Presenting signs can include fever, increased respiratory rate progressing to respiratory distress, and auscultable crackles.

#### Diagnosis

A diagnosis of canine influenza should be considered in all dogs with acute cough until proven otherwise because it is highly transmissible to susceptible dogs. The diagnosis of pneumonia is made by the radiographic detection of a bronchointerstitial or bronchoalveolar pattern or both in dogs showing appropriate clinical signs. A tracheal wash is recommended to determine the types of bacteria involved and their antibiotic sensitivity.

Confirmation of the diagnosis of influenza is possible through several methods: serology, ELISA for antigen detection, virus isolation, and polymerase chain reaction (PCR) for viral RNA. Serology has several advantages compared with the other methods because blood is simple to collect, the resultant serum is stable, and infection can be detected even after viral shedding has ceased. However, rapid confirmation of the diagnosis is not possible through serology

because rising antibody titers are required to confirm the diagnosis. More timely results are possible with antigen detection (Directigen Flu A, Becton, Dickinson and Company) and PCR. Preliminary data by Spindel et al. (2007) using nasal swabs for specimens indicate that PCR is much more sensitive in detecting virus than antigen detection by ELISA or virus isolation. Other specimens that can be submitted for virus isolation or PCR are pharyngeal swabs, tracheal wash fluid, or lung tissue. Results from any test for viral detection can be falsely negative because of the relatively short period of shedding after the development of signs in many patients. For best results, samples are collected from febrile dogs very early in the course of disease.

#### **Treatment**

In dogs with the mild form of disease, cough will generally persist for several weeks even when treated with antibiotics and cough suppressants. Mucopurulent nasal discharge can be a result of secondary bacterial infection and may respond to antibiotics.

Dogs with pneumonia require aggressive supportive care, including intravenous fluid therapy if needed to maintain systemic (and therefore airway) hydration. A variety of bacteria have been isolated from infected dogs, including *Streptococcus equi* subsp. *zooepidemicus* and gram-negative organisms that are resistant to commonly prescribed antibiotics. Broad spectrum antibiotics should be prescribed initially and can be modified later on the basis of culture and sensitivity results and response to therapy. Initial choices include the combination of ampicillin with sulbactam and either a fluoroquinolone or an aminoglycoside or meropenem. (For additional information on treating bacterial pneumonia, see p. 304)

#### **Prognosis**

Most dogs that are exposed to the influenza virus will become infected. Dogs with the mild form of the disease fully recover, although cough may persist for as long as a month. The prognosis is more guarded for dogs that develop the severe form of the disease. Overall mortality has been reported to be <5% (Yoon et al., 2005).

#### **Prevention**

Vaccination is the most promising approach for prevention, but no vaccines are currently available. In veterinary hospitals, animal shelters, and other kenneling facilities, immediate isolation of dogs with signs of influenza is indicated and strict isolation protocols must be followed. The virus is readily killed by routine disinfectants. Successful prevention of spread of organisms depends on careful cleaning and disinfection of tables, cages, bowls, and any other objects in contact with infected dogs. In addition, strict attention to detail is necessary regarding hand cleaning after contact with any animal and using disposable barrier protection (e.g., gloves, booties, outerwear) when working with infected dogs or contaminated areas. Recommendations for managers and workers of kennel facilities are provided by the American

Veterinary Medical Association (www.avma.org/public\_health/influenza/canine\_guidelines.asp).

#### **OTHER VIRAL PNEUMONIAS**

Several other viruses can infect the lower respiratory tract, but rarely do signs of viral pneumonia predominate. The role of canine adenovirus 1 and parainfluenza virus in canine infectious tracheobronchitis has already been discussed (see Chapter 21). In dogs canine distemper virus can also infect the respiratory epithelium. Clinical signs of pneumonia usually result from a secondary bacterial pneumonia. Infection of the gastrointestinal tract or central nervous system can also occur in dogs with distemper (see Chapter 97). In cats, calicivirus can cause pneumonia, but this manifestation of infection is rare. The dry form of feline infectious peritonitis can affect the lungs, but cats are generally seen because of signs of involvement of other organs. Feline infectious peritonitis is discussed in Chapter 97.

#### **BACTERIAL PNEUMONIA**

#### **Etiology**

A wide variety of bacteria can infect the lungs. Common bacterial isolates from dogs and cats with pulmonary infections include Bordetella bronchiseptica, Streptococcus spp., Staphylococcus spp., Escherichia coli, Pasteurella spp., Klebsiella spp., Proteus spp., and Pseudomonas spp. Anaerobic organisms can be part of mixed infections, particularly in animals with aspiration pneumonia or with lung lobe consolidation. Mycoplasma organisms have been isolated from dogs and cats with pneumonia, but their exact role is not known.

Bacteria can colonize the airways, alveoli, or interstitium. The term *pneumonia* means inflammation of the lung, but the term is not specific for bacterial disease. Infection that clinically appears to be limited to the airways and peribronchial tissues is called *bacterial bronchitis*. If all three regions are involved, the disease is called either *bacterial bronchopneumonia* or *bacterial pneumonia*. Most cases of bacterial pneumonia result from bacteria of the oral cavity and pharynx entering the lungs via the airways, which causes a bronchopneumonia involving primarily the gravity-dependent cranial and ventral lung lobes (see Fig. 20-5). Bacteria that enter the lung through the hematogenous route usually cause pneumonia that assumes a caudal or diffuse pattern and marked interstitial involvement.

Bacterial pneumonia is a common lung disease, particularly in dogs. Community-acquired infectious pneumonia has been described in puppies (Radhakrishnan et al., 2007), most often caused by *Bordetella bronchiseptica* (49% of cases). However, consideration should also be given for predisposing abnormalities. *In adult dogs, a predisposing abnormality usually exists*. Abnormalities to consider in all patients include the aspiration of ingested material or gastric contents because of cleft palate, megaesophagus, or other causes of aspiration pneumonia (p. 309); decreased clearance from

the lungs of normally inhaled debris, particularly in animals with chronic bronchitis, ciliary dyskinesia, or bronchiectasis; immunosuppression resulting from drugs, malnutrition, stress, or endocrinopathies; other infections, including canine influenza, canine distemper, feline leukemia virus infection, or feline immunodeficiency virus infection; the inhalation or migration of foreign bodies; and, rarely, neoplasia or fungal or parasitic infections.

#### **Clinical Features**

Dogs and cats with bacterial pneumonia are evaluated because of respiratory signs, systemic signs, or both. Respiratory signs can include cough (which is usually productive and soft), a bilateral mucopurulent nasal discharge, exercise intolerance, and respiratory distress. Cough is less common in cats with pneumonia. Systemic signs include lethargy, anorexia, fever, and weight loss. The animal may have a history of chronic airway disease or regurgitation. Cats, particularly kittens, from stressful housing situations (e.g., overcrowding) appear predisposed to develop pneumonia as a result of Bordetella infections. Dogs with complicated infectious tracheobronchitis may have a recent history of harsh cough and a history consistent with exposure, as described in Chapter 21. Other potential predisposing factors, as listed in the preceding paragraph, are pursued through careful history taking.

Fever may be present on physical examination but is identified in only about half of patients. Crackles and occasionally expiratory wheezes may be auscultated, with the abnormal lung sounds often prominent over the cranioventral lung fields.

#### Diagnosis

Bacterial pneumonia is diagnosed on the basis of the complete blood count (CBC), thoracic radiograph findings, and the results from tracheal wash fluid cytologic analysis and bacterial culture. A CBC showing neutrophilic leukocytosis with a left shift, neutropenia with a degenerative left shift, or moderate-to-marked neutrophil toxicity is supportive of bacterial pneumonia. A normal or stress leukogram is as likely to be found.

Abnormal patterns on thoracic radiographs vary with the underlying disease. The typical abnormality is an alveolar pattern, possibly with consolidation, that is most severe in the dependent lung lobes (see Fig. 20-5). Increased bronchial and interstitial markings are also often present. Infections secondary to foreign bodies can be localized to any region of the lung. An interstitial pattern alone may be present in animals with early or mild disease or in those with infections of hematogenous origin. A bronchial pattern alone may be present in animals with a primarily bronchial infection. Radiographs are also evaluated for the presence of megaesophagus and other extrapulmonary disease.

Pulmonary specimens are evaluated cytologically and microbiologically (bacterial and ideally mycoplasmal cultures) to establish a definitive diagnosis and provide guidance in antibiotic selection. To maximize the diagnostic yield, specimens should be collected before antibiotic therapy is initiated. A tracheal wash specimen is generally sufficient. Septic neutrophilic inflammation is typically found in animals with bacterial pneumonia, and growth of organisms on bacterial culture is expected. Examination of a gramstained preparation will provide early guidance in antibiotic selection pending results of culture and will also assist in the identification of anaerobes or unusual organisms (e.g., *Mycobacteria* and filamentous organisms).

A conscientious effort is also made to identify any underlying problems. In some animals, such as those with megaesophagus, the initiating cause is obvious. Further diagnostic tests are indicated in other animals, depending on the results of the clinicopathologic evaluation. These may include bronchoscopy to search for airway abnormalities or foreign bodies, conjunctival scrapings to look for distemper virus, serologic tests to determine whether the animal has a fungal infection, tests for influenza virus, and hormonal assays to determine whether the animal has hyperadrenocorticism. Ciliary dyskinesia is discussed briefly in Chapter 21. The diagnostic evaluation for aspiration pneumonia is discussed on p. 309.

#### **Treatment**

#### **Antibiotics**

The treatment of bacterial pneumonia consists of antibiotics and supportive care, with follow-up evaluation (Box 22-1). The antibiotic sensitivity of the involved organisms is diffi-



BOX 22-1

Therapeutic Considerations for Bacterial Pneumonia

#### Antibiotics

Selected on basis of results from gram staining and culture and sensitivity testing of pulmonary specimens

#### **Airway Hydration**

Maintain systemic hydration Saline nebulization

#### Physiotherapy

Turning of recumbent animals every 1 to 2 hours Mild exercise of animals in stable condition Coupage

#### **Bronchodilators**

As needed, particularly in cats

#### Oxygen Supplementation

As needed

#### **AVOID**

Diuretics Cough suppressants Corticosteroids

cult to predict. Gram-negative infections and infections with multiple organisms are common. Antibiotics are initially selected on the basis of severity of clinical signs and the cytologic characteristics (i.e., morphology and gram-staining) of organisms found in pulmonary specimens. Antibiotic selection is subsequently modified, as needed, according to clinical response and sensitivity data from bacterial cultures of pulmonary specimens.

The extent to which an antibiotic can penetrate into the airway secretions does not need to be a major consideration in patients with bacterial pneumonia. Antibiotics generally achieve concentrations within the pulmonary parenchyma equal to those in plasma. Nebulization of antibiotics is rarely indicated.

For animals with mild or moderate clinical signs, antibiotics that can be initiated before sensitivity results are available include amoxicillin-clavulanate (20 to 25 mg/kg q8h), cephalexin (20 to 40 mg/kg q8h), or chloramphenicol (dogs, 50 mg/kg q8h; cats, 10 to 15 mg/kg q12h). Fluoroquinolones are reserved for animals with resistant gram-negative infections. Kittens from stressful environments suspected of having Bordetella-induced pneumonia should be treated with amoxicillin-clavulanate, doxycycline (5 to 10 mg/kg q12h; followed by a bolus of water), or fluoroquinolones while awaiting results of cultures. Doxycycline or a fluoroquinolone is more likely to be effective but has a greater potential for side effects in young kittens.

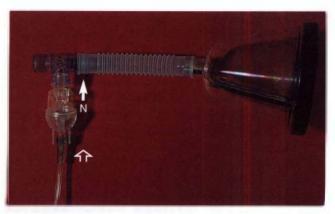
Animals with severe clinical signs or possible sepsis should be treated initially with intravenous antibiotics. Broad-spectrum coverage in animals with life-threatening infections can be achieved with meropenem (8 mg/kg q8h) or the combination of either ampicillin with sulbactam (22 mg/kg of ampicillin q8h) and a fluoroquinolone or ampicillin with sulbactam and an aminoglycoside (e.g., amikacin, 5 to 10 mg/kg q8h). Sulbactam is a beta-lactamase inhibitor, as is clavulanate, and the combination of ampicillin with sulbactam provides a drug with similar activity as amoxicillin-clavulanate in an intravenous formulation. If Toxoplasma infection is among the differential diagnoses, the combination of a fluoroquinolone and clindamycin or a fluoroquinolone and azithromycin can be used (see Chapter 99).

Antibiotic treatment should be continued for at least 1 week after the clinical signs resolve. Guidelines for patient monitoring are provided on p. 306.

#### **Airway Hydration**

The drying of secretions results in increased viscosity and decreased ciliary function, which interfere with the normal clearance mechanisms of the lung. Thus the water content of airway secretions must be maintained and airways must be hydrated in animals with pneumonia. Animals with any evidence of dehydration should receive fluid therapy. Diuretics can cause dehydration, and their use is contraindicated in such animals.

Additional moisture for the airways can be provided through humidification or nebulization. Such therapy is par-



Disposable jet nebulizers are readily available and inexpensive. Sterile saline solution is placed in the nebulizer (N). Oxygen enters the bottom of the nebulizer (open arrow), and nebulized air exits the top (closed arrow). Nebulized air is delivered to the animal with a face mask, as shown here, or it can be delivered into an enclosed cage.

ticularly recommended for animals with areas of consolidation or with suspected decreased airway clearance, such as those with bronchiectasis. Humidification refers to the saturation of air with water vapor. Depending on the temperature, the volume of water that remains as vapor is limited. The moisture reaches only the nasal cavity and the proximal trachea. Vaporization is not effective in hydrating deeper regions of the lungs. However, the more proximal effect can still provide some relief, particularly in animals with nasal discharge. Humidification is convenient and can be achieved simply by placing the animal in a steamy bathroom or in a small room with an inexpensive vaporizer, which is readily available at pharmacies.

Nebulization is necessary to provide moisture deeper into the airways. Nebulizers generate small, variably sized droplets, with a diameter ranging from 0.5 to 5 µm required to reach the deeper airways. Several types of nebulizers are available. Disposable jet nebulizers are readily available and inexpensive, and they can be attached to bottled oxygen or an air compressor (Fig. 22-1). Effective, inexpensive portable compressors are commercially available if needed for home use. The nebulized oxygen is delivered to the animal through a face mask. The particles can be seen as a mist.

Sterile saline solution is used as a nebulizing solution because it has mucolytic properties and is relatively nonirritating. Premedication with bronchodilators has been suggested as a way to reduce the bronchospasms, although use of saline alone in dogs does not usually cause problems. It is recommended that nebulization be performed two to six times daily for 10 to 30 minutes each time. Nebulization should be followed immediately by physiotherapy to promote the expectoration of exudate that may have increased in volume with rehydration. Nebulizers and tubing should be replaced after no more than 24 hours of use in actively infected patients, and face masks should be cleaned and disinfected.

#### **Physiotherapy**

Lying in one position impairs airway clearance, and lung consolidation can occur if one side remains dependent for prolonged periods. Therefore animals that are recumbent must be turned at least every 2 hours. Because activity causes animals to take deeper breaths and to cough, which promotes airway clearance, animals that are in a sufficiently stable condition and can tolerate the oxygen demands should be mildly exercised.

Physiotherapy is indicated after nebulization to promote coughing and facilitate the clearance of exudate from the lungs. Mild exercise is used when possible. Otherwise, coupage is performed. To perform coupage, the clinician strikes the animal's chest over the lung fields with cupped hands. The action should be forceful but not painful and should be continued for 5 to 10 minutes if tolerated by the patient. Coupage may also be beneficial for animals with lung consolidation that are not receiving nebulization.

#### **Bronchodilators**

Bronchospasm can occur secondary to inflammation, particularly in cats. Bronchodilators are used in animals showing increased respiratory efforts, particularly if expiratory wheezes are auscultated. Patient status should be monitored closely because bronchodilators may worsen ventilation:perfusion  $(\dot{V}/\dot{Q})$  mismatching, exacerbating hypoxemia. They are discontinued if clinical signs worsen or do not improve. Bronchodilators are discussed in Chapter 21 (cats, p. 290; dogs, p. 296).

#### Other Treatment

Expectorants are of questionable value in dogs and cats. Glucocorticoids are relatively contraindicated in animals with bacterial pneumonia. Oxygen therapy (see Chapter 27) is provided if the clinical signs, arterial blood gas measurements, or pulse oximetry measurements indicate a need for it.

#### Monitoring

Dogs and cats with bacterial pneumonia should be closely monitored for signs of deteriorating pulmonary function. Respiratory rate and effort and mucous membrane color are monitored at least twice daily. Thoracic radiographs and the CBC are evaluated every 24 to 72 hours. If the animal's condition does not improve within 72 hours, it may be necessary to alter treatment or perform additional tests. Animals showing improvement are sent home and reevaluated every 10 to 14 days. Once clinical and radiographic signs have resolved, antibiotic treatment is continued for an additional week.

The evidence of infection on initial radiographs can obscure that of focal disease processes such as neoplasia or foreign bodies, and focal opacities may not be apparent while an animal is receiving antibiotics. Therefore radiographs should be reevaluated approximately I week after antibiotic therapy has been discontinued in animals with recurrent infection or suspected localized disease. Persistence of local-

ized disease after long-term antibiotic therapy is an indication for bronchoscopy, thoracoscopy, or thoracotomy.

#### **Prognosis**

Bacterial pneumonia responds readily to appropriate therapy. The prognosis is more guarded in animals with underlying problems that predispose them to infection, and the likelihood of eliminating these problems must be taken into consideration.

Pulmonary abscess formation is an uncommon complication of bacterial pneumonia. Abscesses are seen as focal lesions on radiographs, and entire lobes may be involved. Horizontal-beam radiographs can be useful in determining whether the lesions are filled with fluid. Ultrasonography can also be helpful in characterizing areas of consolidation. Abscesses resolve in response to prolonged medical therapy in some animals, but if improvement is not observed or radiographic evidence of disease reappears after the discontinuation of therapy, surgical excision (i.e., lobectomy) is indicated.

#### **TOXOPLASMOSIS**

The lungs are a common site of involvement in cats with toxoplasmosis. Thoracic radiographs typically show fluffy alveolar and interstitial opacities throughout the lungs in such animals. Less often, a nodular interstitial, diffuse interstitial or bronchial pattern, lung lobe consolidation, or pleural effusion is seen. Organisms are rarely recovered from the lungs by tracheal wash. Bronchoalveolar lavage is more likely to retrieve organisms (see Fig. 20-17). Toxoplasmosis is a multisystemic disease and is discussed in detail in Chapter 99.

#### **FUNGAL PNEUMONIA**

The common mycotic diseases that can involve the lungs are blastomycosis, histoplasmosis, and coccidioidomycosis. In most cases, the organisms enter the body through the respiratory tract. The infection may be successfully eliminated without the animal showing clinical signs, or the animal may show only transient respiratory signs. The infection may also progress to cause disease involving the lungs alone or spread systemically to various target organs, or both processes may occur. Cryptococcal organisms also enter the body through the respiratory tract and can infect the lungs, particularly in cats. However, the presenting signs in cats are generally those of nasal infection. Pulmonary signs are most often the primary presenting complaint in dogs with blastomycosis and cats with histoplasmosis.

Pulmonary mycoses are considered in the differential diagnoses of dogs or cats with progressive signs of lower respiratory tract disease, especially if they occur in conjunction with weight loss, fever, lymphadenopathy, chorioretinitis, or other evidence of multisystemic involvement. Thoracic

radiographs typically show a diffuse, nodular, interstitial pattern of the lungs (see Fig. 20-6). The nodules are often miliary. The presence of this pattern in dogs with suspicious clinical signs supports a diagnosis of mycotic infection, but other diseases, including neoplasia, parasitic, or atypical bacterial (e.g., mycobacterial) infections and eosinophilic lung disease, can also produce similar patterns, so these must be borne in mind as well. Other potential radiographic abnormalities include alveolar and bronchointerstitial patterns and consolidated regions of lung. Hilar lymphadenopathy can occur, most commonly in animals with histoplasmosis. The lesions caused by histoplasmosis can also be calcified.

Organisms can occasionally be retrieved by tracheal wash. However, because of the interstitial nature of these diseases, bronchoalveolar lavage and lung aspiration are more likely to be successful (see Figs. 20-15 and 20-16). Fungal culture is probably more sensitive than cytologic analysis alone. An inability to find organisms in pulmonary specimens does not rule out the diagnosis of mycotic disease, however. A complete discussion of systemic mycoses is provided in Chapter 98.

#### **PULMONARY PARASITES**

Several parasites can cause lung disease. Certain intestinal parasites, especially *Toxocara canis*, can cause transient pneumonia in young animals, usually those younger than a few months of age, as the larvae migrate through the lungs. Infection with *Dirofilaria immitis* can result in severe pulmonary disease through inflammation and thrombosis (see Chapter 10). *Oslerus osleri* resides at the carina and mainstem bronchi of dogs and is discussed in Chapter 21. The other primary lung parasites that are most commonly diagnosed are *Capillaria* (*Eucoleus*) aerophila and *Paragonimus kellicotti* in dogs and cats, *Aelurostrongylus abstrusus* in cats, and *Crenosoma vulpis* in dogs.

Infection occurs as a result of the ingestion of infective forms, often within intermediate or paratenic hosts, that subsequently migrate to the lungs. An eosinophilic inflammatory response often occurs within the lungs, causing clinical signs in some, but not all, infected animals. The definitive diagnosis is made by the identification of the characteristic eggs or larvae in respiratory or fecal specimens (see Chapter 20).

#### CAPILLARIA (EUCOLEUS) AEROPHILA

Capillaria aerophila, also known as Eucoleus aerophila, is a small nematode. Adult worms are located primarily beneath the epithelial surfaces of the large airways. Clinical signs develop in very few animals with Capillaria infections, and the disease is most often identified through the fortuitous identification of characteristic eggs during routine fecal examinations.

The rare animal that displays signs has signs of allergic bronchitis. Thoracic radiograph findings are generally normal, although a bronchial or bronchointerstitial pattern may be seen. Tracheal wash fluid can show eosinophilic inflammation. *Capillaria* is diagnosed by the finding of characteristic eggs in tracheal wash fluid or fecal flotation material (see Fig. 20-12, *C*).

The treatment of choice for dogs and cats is fenbendazole (50 mg/kg orally q24h for 14 days). Levamisole (8 mg/kg orally for 10 to 20 days) has also been used successfully in dogs. Ivermectin has been suggested for treatment, but a consistently effective dosage has not been established. The prognosis in animals with the disease is excellent.

#### PARAGONIMUS KELLICOTTI

Paragonimus kellicotti is a small fluke. Snails and crayfish are both necessary intermediate hosts, thus limiting the disease to animals that have been in the region of the Great Lakes, in the Midwest, or in the southern United States. Pairs of adults are walled off by fibrous tissue, usually in the caudal lung lobes, with a connection to an airway to allow for the passage of eggs. A local granulomatous reaction may occur around the adults, or a generalized inflammatory response to the eggs may occur.

Infection is more common in cats than in dogs. Some dogs and cats have no clinical signs. When clinical signs are present, they may be the same as those seen in animals with allergic bronchitis. Alternatively, signs of spontaneous pneumothorax can result from the rupture of cysts.

The classic radiographic abnormality is single or multiple solid or cavitary mass lesions, most commonly present in the right caudal lobe (see Fig. 20-10). Other abnormal patterns seen on thoracic radiographs can be bronchial, interstitial (reticular or nodular), or alveolar in nature, depending on the severity of the inflammatory response (see Fig. 20-11).

Infection is diagnosed definitively through the identification of the ova in fecal specimens (using the sedimentation technique described in Chapter 20), tracheal wash fluid, or bronchoalveolar lavage fluid (see Fig. 20-12, *D*). Multiple fecal specimens should be examined in suspected cases because the eggs are not always present. A presumptive diagnosis is necessary in some cases. Note that ova from the tapeworm *Spirometra* spp. can be mistakenly identified as ova from *Paragonimus* (Fig. 22-2).

Fenbendazole is used to treat paragonimiasis at the same dosage as that recommended for the treatment of capillariasis. Alternatively, praziquantel can be used at a dosage of 23 mg/kg orally every 8 hours for 3 days.

Thoracocentesis should be used to stabilize the condition of animals with pneumothorax. If air continues to accumulate within the pleural space, however, it may be necessary to place a chest tube and perform suction until the leak has been sealed (see Chapter 24). Surgical intervention is rarely required.

The response to treatment is monitored by thoracic radiographs and periodic fecal examinations. Treatment may have to be repeated in some cases. The prognosis is excellent.



FIG 22-2
The operculated ova from Spirometra tapeworms (A) can be misdiagnosed as Paragonimus ova (B). The Spirometra ova are smaller and more pale than the yellow-brown Paragonimus ova. Most notably, Paragonimus ova have a distinctly visible shoulder (arrow) at the operculated end. (Courtesy James R. Flowers.)

#### **AELUROSTRONGYLUS ABSTRUSUS**

Aelurostrongylus abstrusus is a small worm that infects the small airways and pulmonary parenchyma of cats. Snails or slugs serve as intermediate hosts. Most cats with infection have no clinical signs. Those cats that do are usually young. The clinical signs are those of bronchitis. The abnormalities seen on radiographs may also reflect bronchitis, although a diffuse miliary or nodular interstitial pattern is present in some cats. Eosinophilic inflammation may be apparent in peripheral blood and airway specimens.

A definitive diagnosis is made through the identification of larvae, which may be present in fecal specimens prepared using the Baermann technique (see Fig. 20-12, A) or in airway specimens obtained by tracheal washing or bronchoalveolar lavage. Multiple fecal specimens should be examined in suspected cases because the larvae are not always present.

Cats should be treated with fenbendazole at the same dosage as that used for the treatment of capillariasis. In one study, the dosage of 50 mg/kg orally q24h for 15 days was effective in eliminating infection in all four cats treated (Grandi et al., 2005). In contrast with a previous report, ivermectin (0.4 mg/kg, administered subcutaneously) was not effective in one cat treated. The response to treatment is monitored by thoracic radiographs and periodic fecal examinations. Treatment may have to be repeated in some cases.

Antiinflammatory therapy with glucocorticoids alone often causes the clinical signs to resolve. However, eliminating the underlying parasitic disease is a preferable treatment

goal, and glucocorticoid therapy may interfere with the effectiveness of the antiparasitic drugs. Bronchodilators may provide symptomatic relief and presumably do so without interference with antiparasitic drug action. The prognosis in animals with the infection is excellent.

#### CRENOSOMA VULPIS

Crenosoma vulpis is a lungworm of foxes that can also infect dogs. Dogs living in Atlantic Canada and parts of Europe are most commonly diagnosed with this disease, while the diagnosis remains rare in the United States. However, it is possible that with increased residential development into fox habitats, the frequency of cases in this country will increase. The worm resides in the airways (i.e., trachea, bronchi, bronchioles). Snails or slugs serve as intermediate hosts. The clinical signs are those of allergic or chronic bronchitis. Thoracic radiographs may have a bronchointerstitial or patchy alveolar pattern or occasionally a nodular pattern. Infection is diagnosed definitively through the identification of the larvae in fecal specimens using the Baermann technique described in Box 20-8, tracheal wash fluid, or bronchoalveolar lavage fluid (see Fig. 20-12, B). Multiple fecal specimens should be examined in suspected cases because the larvae are not always present. A single oral dose of milbemycin oxime (0.5 mg/kg) was effective in resolving clinical signs and elimination of larvae from feces collected 4 to 6 weeks after treatment in 32 dogs (Conboy, 2004). This treatment may not be effective against immature larvae. As with other pulmonary parasites, the response to treatment is monitored with thoracic radiographs and periodic fecal examinations.

#### **ASPIRATION PNEUMONIA**

#### Etiology

A small amount of fluid and bacteria is aspirated from the oropharynx into the airways of healthy animals, but normal airway clearance mechanisms prevent infection. Organisms from the oropharynx are thought to be the source of bacteria in many animals with bacterial pneumonia, specifically bacterial bronchopneumonia (see p. 303). In people such infection is termed aspiration pneumonia. In veterinary medicine the term aspiration pneumonia is generally used to refer to the inflammatory lung disease that occurs as a result of the inhalation of overt amounts of solid or liquid material into the lungs. The materials that are usually aspirated are stomach contents or food. Normal laryngeal and pharyngeal function prevents aspiration in healthy animals, although occasionally an excited puppy or a dog running through tall grass aspirates a foreign body. Otherwise, the presence of aspiration pneumonia in an animal of any age indicates an underlying predisposing abnormality (Box 22-2).

Aspiration pneumonia is a common complication of animals with regurgitation. Megaesophagus is the most common cause of regurgitation (see Chapter 31). Other causes of regurgitation (e.g., reflux esophagitis, esophageal obstruction) are less common. Another cause of aspiration pneumonia is localized or systemic neurologic or muscular disease affecting the normal swallowing reflexes of the larynx or pharynx. These reflexes can also be depressed in dogs or cats with abnormal levels of consciousness or in those that are anesthetized. Laryngeal paralysis does not always lead to the development of aspiration pneumonia, but aspiration is a potential complication of therapeutic laryngoplasty. It can also occur in animals with abnormal pharyngeal anatomy resulting from mass lesions, brachycephalic airway syndrome, or cleft palate. Bronchoesophageal fistulae are a rare cause of aspiration pneumonia.

Aggressive force-feeding, especially in mentally depressed animals, and improper placement of stomach tubes into the trachea are iatrogenic causes of aspiration pneumonia. Mineral oil administered to prevent hairballs can be a cause of aspiration pneumonia in cats because the tasteless and odorless oil is poorly handled by the pharynx.

The damage to the lung resulting from aspiration may stem from chemical damage, obstruction of the airways, infection, and the resulting inflammatory response to each of these factors. Gastric acid causes severe chemical injury to the lower airways. Tissue necrosis, hemorrhage, edema, and bronchoconstriction ensue, and a marked acute inflammatory response is initiated. Hypoxemia resulting from decreased alveolar ventilation and compliance can be fatal.

Severe respiratory distress can occur from physical obstruction of the airways by the aspirated material. In most cases only small airways are obstructed, but rarely a large piece of food will obstruct a major airway. Obstruction is subsequently exacerbated by reflex bronchoconstriction and inflammation. Inhaled solid material initiates an inflammatory reaction that includes an abundance of macrophages.



**B**OX 22-2

Underlying Causes of Aspiration Pneumonia in Dogs and Cats\*

#### **Esophageal Disorders**

Megaesophagus, Chapter 31 Reflux esophagitis, Chapter 31 Esophageal obstruction, Chapter 31 Myasthenia gravis (localized), Chapter 71 Bronchoesophageal fistulae

#### **Localized Oropharyngeal Abnormalities**

Cleft palate

Cricopharyngeal motor dysfunction, Chapter 31

Laryngoplasty, Chapter 17

Brachycephalic airway syndrome, Chapter 17

#### Systemic Neuromuscular Disorders

Myasthenia gravis, Chapter 71 Polyneuropathy, Chapter 71 Polymyopathy, Chapter 72

#### **Decreased Mentation**

General anesthesia Sedation Post ictus, Chapter 67 Head trauma Severe metabolic disease

#### latrogenic\*\*

Force-feeding Stomach tubes, Chapter 30

#### **Vomiting (in Combination with Other Predisposing** Factors), Chapter 28

- \* Discussions of these abnormalities can be found on the given chapter numbers.
- \*\*Overzealous feeding, incorrect tube placement, or loss of lower esophageal sphincter competence because of presence of tube.

This response can become organized, resulting in the formation of granulomas.

Bacterial infection may result from the aspiration of contaminated material, such as ingesta that remained in the esophagus. Acidic gastric contents are probably sterile, although in people the contents are considered contaminated if antacids have been taken, if an intestinal obstruction is present, or with periodontal disease. Note that many veterinary patients have periodontal disease. Regardless of the sterility of the aspirated material, the resultant damage to the lungs by gastric acid greatly predisposes the animal to the development of a secondary infection.

The inhalation of mineral oil elicits a chronic inflammatory response. The clinical signs in this setting are often mild, but in rare instances they may be severe. Radiographic abnormalities persist and can be erroneously interpreted as representing neoplastic lesions.

#### **Clinical Features**

Dogs and cats with aspiration pneumonia are frequently presented for acute, severe respiratory signs. Systemic signs such as anorexia and depression are common, and these patients may even present in shock. Vomiting, regurgitation, or eating may have preceded the onset of distress. Other patients are seen because of chronic intermittent or progressive signs of coughing or increased respiratory efforts. Occasionally, patients show only signs of depression or the predisposing disease. A thorough history is obtained, with all organ systems carefully reviewed. The owners are specifically questioned about force-feeding and medication administration.

Fever may be present, but it is an inconsistent finding. Crackles are often auscultated, particularly over the dependent lung lobes. Wheezes are heard in some cases. Once a patient is in stable condition, a thorough neuromuscular examination is performed. The ability of the patient to prehend and swallow food and water should also be observed.

#### **Diagnosis**

Aspiration pneumonia is usually diagnosed on the basis of the suggestive radiographic findings in conjunction with evidence of a predisposing condition. Thoracic radiographs typically show diffuse, increased interstitial opacities with alveolar flooding (air bronchograms) and consolidation of the dependent lung lobes (see Fig. 20-5). Radiographic abnormalities may not be apparent until 12 to 24 hours after aspiration, however. Occasionally, nodular interstitial patterns are seen in chronic cases. Large nodules can form around solids; miliary nodules often form in animals that have aspirated mineral oil. Large airway obstruction is suspected if radiographs show a soft-tissue mass within a large airway, but this is an unusual finding. A marked, diffuse alveolar pattern can be seen in dogs that have severe secondary edema (see the section on pulmonary edema, p. 319).

The peripheral blood count can reflect the pulmonary inflammatory process, but it is often normal. Neutrophils are examined for the presence of toxic changes suggestive of sepsis.

Tracheal wash is indicated for all animals that can tolerate the procedure to identify complicating bacterial infection and obtain antibiotic sensitivity data. A marked inflammatory response characterized by a predominance of neutrophils is seen in cytologic specimens. Blood resulting from hemorrhage may be seen in specimens from animals in the acute period after aspiration. Bacteria may also be seen. Bacterial cultures should always be performed.

Bronchoscopy can be used to grossly examine the airways and detect and remove large solids. However, the likelihood of a large airway obstruction is very small, so bronchoscopy is performed only if there are clear signs of large airway obstruction (see Chapter 26) or if the animal is not conscious and therefore does not require general anesthesia for the procedure.

Blood gas analysis can be helpful in differentiating hypoventilation from ventilation-perfusion abnormalities (see Chapter 20), although a combination of abnormalities exists in most animals with aspiration pneumonia. Animals with evidence of profound hypoventilation may have either a large airway obstruction or muscle weakness secondary to an underlying neuromuscular disorder such as myasthenia gravis. Blood gas analysis also assists in the therapeutic management of these animals and can be used effectively to monitor the response to therapy.

Diagnostic evaluation is indicated to identify potential underlying diseases (see Box 22-2). This may include a thorough oral and pharyngeal examination, contrast-enhanced radiographic studies to evaluate the esophagus, or specific neuromuscular tests.

#### **Treatment**

Suctioning of the airways is helpful only for animals that aspirate in the hospital while already anesthetized or unconscious, when it can be performed immediately after aspiration. If a bronchoscope is immediately available, suctioning can be performed through the biopsy channel, which affords visualized guidance. Alternatively, a sterile soft rubber tube attached to a suction pump can be passed blindly into the airways through an endotracheal tube. Excessive suction may result in lung lobe collapse. Therefore low-pressure, intermittent suction is used, followed by expansion of the lungs with several positive-pressure ventilations using an anesthetic or Ambu bag. Airway lavage is contraindicated.

Animals in severe respiratory distress should be treated with fluid therapy, oxygen supplementation, bronchodilators, and glucocorticoids. Fluids are administered intravenously at high rates to treat shock (see Chapter 30) and should be continued after initial stabilization of the animal's condition to maintain systemic hydration, which is necessary to maximize the effectiveness of airway clearance mechanisms. However, overhydration must be avoided because of a tendency for pulmonary edema.

Oxygen supplementation (see Chapter 27) is initiated immediately in compromised animals. Positive-pressure ventilation is required for animals in severe respiratory distress that is unresponsive to oxygen therapy.

Bronchodilators can be administered to decrease bronchospasms and ventilatory muscle fatigue. They are most likely to be effective in cats. Bronchodilators can worsen ventilation:perfusion  $(\dot{V}/\dot{Q})$  mismatching, exacerbating hypoxemia. They are discontinued if no improvement is seen or clinical signs appear to worsen after their administration.

Rapid-acting glucocorticoids are administered for the treatment of shock. Their use in the absence of shock is controversial. The antiinflammatory effects of glucocorticoids can be beneficial, but glucocorticoids can interfere with normal host defense mechanisms in tissues that have already been severely compromised. This author reserves the use of glucocorticoids for patients that have severe respiratory

compromise and a deteriorating clinical picture despite appropriate antibiotic therapy and supportive care. Low (antiinflammatory) doses of short-acting preparations are administered for up to 48 hours.

Animals with a large airway obstruction can benefit from bronchoscopy and foreign body removal. However, routine bronchoscopy is not indicated because of the risk of the general anesthesia needed during the procedure and the infrequency of large airway obstructions.

Antibiotics are administered immediately in animals that are presented in severe distress or with overt systemic signs of sepsis. Selected antibiotics should have a broad spectrum of activity and be administered intravenously. Such drugs include meropenem or combinations of either ampicillin with sulbactam and a fluoroquinolone or ampicillin with sulbactam and an aminoglycoside (see the section on bacterial pneumonia, p. 303).

A tracheal wash is performed in stable patients before initiation of antibiotics to document the presence of infection and obtain antibiotic sensitivity data. This information is particularly valuable because prolonged treatment is often needed and also because research in human medicine has amply demonstrated that resistant secondary infections can develop after aspiration in patients given antibiotics initially or on an empirical basis. As discussed for bacterial pheumonia, the high incidence of gram-negative and mixed infections make assumptions regarding antibiotic sensitivity prone to error. Pending results of culture, it is reasonable to initiate treatment with a penicillin with a beta-lactamase inhibitor (e.g., amoxicillin-clavulanate or ampicillin with sulbactam). Because infection can occur as allater complication in these patients, frequent monitoring with physical examination, CBC, and thoracic radiographs is necessary to detect any deterioration consistent with secondary infection. Tracheal wash is repeated if infection is suspected.

Further therapeutic and monitoring considerations are discussed in the section on bacterial pneumonia (p. 303). Underlying diseases are treated to prevent recurrence.

#### **Prognosis**

Animals with mild signs of disease and a correctable underlying problem have an excellent prognosis. The prognosis is worse for animals with more severe disease or uncorrectable underlying problems.

#### EOSINOPHILIC LUNG DISEASE (PULMONARY INFILTRATES WITH EOSINOPHILS AND EOSINOPHILIC PULMONARY GRANULOMATOSIS)

Eosinophilic lung disease is a broad term describing inflammatory lung disease in which the predominant infiltrating cell is the eosinophil. Eosinophilic inflammation can involve primarily the airways or the interstitium. Allergic bronchitis and idiopathic bronchitis are by far the most common eosinophilic lung diseases seen in cats and are discussed in Chapter 21. Interstitial infiltration, with or without concurrent bronchitis, is sometimes referred to as *pulmonary infiltrates with eosinophils (PIE)* and is typically seen in dogs. *Eosinophilic pulmonary granulomatosis* is a severe type of PIE seen in dogs and is characterized by the development of nodules and often hilar lymphadenopathy. It must be differentiated from a mycotic infection and neoplasia. The term *eosinophilic bronchopneumopathy* is also used to describe eosinophilic lung disease. These names are descriptive only and likely encompass a variety of hypersensitivity disorders of the lung.

Because eosinophilic inflammation is a hypersensitivity response, an underlying antigen source is actively pursued in affected animals. Considerations include heartworms, pulmonary parasites, drugs, and inhaled allergens. Food allergy could play a role in these disorders, but this association has not been explored. Potential allergens are discussed further in the section on allergic bronchitis, Chapter 21. Bacteria, fungi, and neoplasia can also induce a hypersensitivity response, but this response often is not the predominant finding. In many cases no underlying disease can be found. Eosinophilic pulmonary granulomatosis is strongly associated with heartworm disease.

#### Clinical Features

Eosinophilic lung diseases are seen in young and older dogs. Affected dogs are evaluated because of progressive respiratory signs, such as cough, increased respiratory efforts, and exercise intolerance. Systemic signs such as anorexia and weight loss are usually mild. Lung sounds are often normal, although crackles or expiratory wheezes are possible.

#### **Diagnosis**

The finding of peripheral eosinophilia is included in some definitions of PIE, but it is not present in all animals with the disease, nor is it a specific finding. A diffuse interstitial pattern is seen on thoracic radiographs. Eosinophilic pulmonary granulomatosis results in the formation of nodules, usually with indistinct borders. These nodules can be quite large, and hilar lymphadenopathy may also be present. A patchy alveolar opacity and consolidation of the lung lobes can occur as well.

Pulmonary specimens must be examined to establish a diagnosis of PIE. In some cases of PIE, evidence of eosino-philic inflammation may be found in tracheal wash fluid. More aggressive techniques for collecting pulmonary specimens, such as bronchoalveolar lavage, lung aspiration, or lung biopsy, are required to identify the eosinophilic response in other cases. Other inflammatory cell populations are frequently present in lesser numbers in such specimens.

Potential antigen sources should be considered, and pulmonary specimens should be carefully examined for the presence of infectious agents and features of malignancy. Heartworm tests and fecal examinations for pulmonary parasites are indicated in all cases.

#### **Treatment**

Any primary disease identified during the diagnostic evaluation of these animals is treated directly. Eliminating the source of the antigen that may be triggering the excessive immune response may result in a cure.

Antiinflammatory therapy with glucocorticoids is indicated for dogs in which an antigen source cannot be identified and for dogs with heartworm disease if the cosin-ophilic inflammation is causing respiratory compromise (see Chapter 10). Dogs with eosinophilic granulomatosis often require more aggressive immunosuppressive therapy.

Dogs are typically treated with glucocorticoids, such as prednisone, at an initial dosage of 1 to 2 mg/kg orally every 12 hours. Clinical signs and thoracic radiographs are used to monitor the animal's response to therapy, and initially these should be assessed every week. Once the clinical signs have resolved, the dosage of glucocorticoids is decreased to the lowest effective one. If signs have remained in remission for 3 months, discontinuation of therapy can be attempted. If signs are exacerbated by glucocorticoid therapy, immediate reevaluation to search for underlying infectious agents is indicated.

Dogs with large nodular lesions (eosinophilic granulomatosis) should be treated with a combination of glucocorticoids and a cytotoxic agent. Prednisone is administered to these animals at a dosage of 1 mg/kg orally every 12 hours, in combination with cyclophosphamide at a dosage of 50 mg/m<sup>2</sup> orally every 48 hours. Clinical signs and thoracic radiographs are evaluated every 1 to 2 weeks until remission is achieved. CBCs are also done every 1 to 2 weeks to detect excessive bone marrow suppression resulting from the cyclophosphamide. Attempts to discontinue therapy can be made after several months of remission. It may be necessary to discontinue the cyclophosphamide earlier than this because long-term treatment is associated with sterile hemorrhagic cystitis. (See Chapter 78 for further discussion of the adverse effects of cyclophosphamide therapy.) The effectiveness of other immunosuppressive drugs, such as cyclosporine, have not been reported,

#### **Prognosis**

A wide spectrum of disease is seen in terms of both the severity of the signs and the underlying causes. The prognosis is generally fair to good. However, the prognosis is guarded in dogs with severe eosinophilic pulmonary granulomatosis.

#### IDIOPATHIC INTERSTITIAL PNEUMONIAS

The term *idiopathic interstitial pneumonia* generally denotes inflammatory and/or fibrotic infiltration of the lungs involving primarily the alveolar septa. Small airways, alveoli, and the pulmonary vasculature may also be affected. The alveolar

septa include alveolar epithelium, epithelial basal lamina, capillary endothelial basal lamina, and capillary endothelium. Other cells include fibroblasts and alveolar macrophages. To make a diagnosis of idiopathic disease, the known etiologies of interstitial lung disease must be ruled out as completely as possible. Etiologies of interstitial lung disease are numerous and include many infectious agents and some toxins and neoplasia.

Idiopathic pulmonary fibrosis is the most well-described idiopathic interstitial pneumonia in dogs and cats. Some of the eosinophilic lung diseases (not including allergic or idiopathic feline bronchitis) may also be part of this group of diseases (see p. 311). Other inflammatory lung diseases of the interstitium in which a cause cannot be identified are occasionally seen in dogs and cats. The lesions may represent a form of vasculitis, a component of systemic lupus erythematosus, immune complex disease, or some other hypersensitivity response. These diseases are rare, however, and not well documented. A lung biopsy must be performed for a definitive diagnosis to be made. A clinical diagnosis is made only after extensive testing has been done to rule out more common causes of lung disease, particularly infectious agents and neoplasia, and after a prolonged positive response to immunosuppressive therapy. Lymphomatoid granulomatosis is a nodular interstitial disease that exhibits clinical signs similar to those seen in animals with eosinophilic pulmonary granulomatosis. It was initially considered to be an inflammatory lung disease but is currently considered to be lymphoproliferative neoplasia of the lung (see p. 314).

#### **IDIOPATHIC PULMONARY FIBROSIS**

In people idiopathic pulmonary fibrosis is the clinical diagnosis that is defined by the histopathologic diagnosis of usual interstitial pneumonia. However, the histopathologic pattern of usual interstitial pneumonia can be seen as a result of other diseases, and according to the American Thoracic Society/European Respiratory Society consensus statement (2002), the diagnosis of idiopathic pulmonary fibrosis also requires (1) the exclusion of other known causes of interstitial lung diseases including drug toxicities, environmental exposures, and collagen vascular diseases; (2) characteristic radiographic or computed tomographic abnormalities; and (3) characteristic pulmonary function abnormalities. In veterinary medicine the latter criterion may be difficult to apply, but attention should be paid to the other criteria.

The characteristic lesions that result in the histopathologic pattern of usual interstitial pneumonia are as follows: fibrosis, areas of fibroblast proliferation, metaplasia of the alveolar epithelium, and mild to moderate inflammation. Honeycomb change may occur as a result of enlarged airspaces lined by abnormal alveolar epithelium. The lungs are heterogeneously affected, with areas of normal lung intermixed with abnormal regions. The abnormal regions are often subpleural. A defect in wound healing has been hypothesized as the cause.

Idiopathic pulmonary fibrosis has been recently described in cats on the basis of histologic lesions which are quite

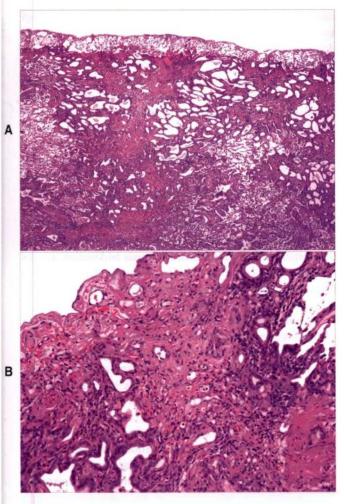


FIG 22-3

Photomicrographs of a lung biopsy from a cat with idiopathic pulmonary fibrosis. At lower power (A) there is distortion and obliteration of the normal pulmonary architecture because of replacement of the parenchyma with disorganized bands of fibrous tissue and scattered mononuclear inflammatory cells. There are few recognizable alveoli in this section. The alveolar septae are thickened, and metaplasia of the alveolar epithelium is present. At higher power (B) subpleural alveoli show marked distortion with marked septal fibrosis and type 2 epithelial hyperplasia. Although normal areas of the lung are not shown, the disease is characterized by heterogeneity of lesions within the lung. (Photomicrographs courtesy Stuart Hunter.)

similar to those in people (Cohn et al., 2004; Williams et al., 2006; Fig. 22-3). Unlike the disease that affects people and cats, the disease in dogs has been associated with the primary lesion of collagen deposition in the alveolar septa with no fibroblastic foci (Norris et al., 2005).

Neoplasia can occur concurrently with idiopathic pulmonary fibrosis in people and was reported in 6 of 23 cats (Cohn et al., 2004). The lesions of pulmonary fibrosis can also be misinterpreted as carcinoma, and 4 of 23 cats considered to have pulmonary fibrosis were initially given a pathologic diagnosis of carcinoma.

#### **Clinical Features**

A breed predisposition is seen in dogs with pulmonary fibrosis. West Highland White Terriers are most frequently reported, with fewer cases documented among Staffordshire Bull Terriers, Jack Russell Terriers, Cairn Terriers, and Schipperkes. Both dogs and cats tend to be middle-aged or older at the time of presentation, although characteristic signs have been found in patients as young as 2 years of age.

Signs are most often slowly progressive over months. In cats the duration of signs may be shorter, with 6 of 23 cats having shown signs for only 2 days to 2 weeks (Cohn et al., 2004). Respiratory compromise is the most prominent clinical sign of pulmonary fibrosis, manifested as exercise intolerance and/or rapid, labored breathing. Cough often occurs, but if it is the predominant sign, higher consideration for a diagnosis of bronchitis should be given. Syncope may occur in dogs.

Crackles are the hallmark auscultatory finding in dogs and are noted in some cats. Wheezes are heard in approximately half of dogs and some cats. The abnormal breathing pattern is typically tachypnea with relatively effortless expiration.

#### **Diagnosis**

Thoracic radiographs of dogs with pulmonary fibrosis typically show a diffuse interstitial pattern. The abnormal densities generally must be moderate to severe to be distinguished from age-related change. A bronchial pattern is often noted concurrently, contributing to the overlap in signs between pulmonary fibrosis and chronic bronchitis. Evidence of pulmonary hypertension may be seen (see p. 316). Radiographs of cats with this disease may show diffuse or patchy infiltrate (Fig. 22-4). Patterns may be interstitial, bronchial, alveolar, or mixed but are often quite severe. Bronchiectasis, caused by traction on the airways, may be noted in either species with advanced disease.

Results of the CBC, serum biochemistry panel, and urinalysis are generally unremarkable. Polycythemia may be present secondary to chronic hypoxemia. Screening tests to identify other etiologies of interstitial lung disease include fecal examinations for parasites, heartworm tests, and appropriate infectious disease serology.

Airway specimens should be collected in sufficiently stable patients, primarily to assist in the identification of other causes of lung disease. Mild to moderate inflammation may be seen in patients with pulmonary fibrosis, but this is a nonspecific finding. Bronchoscopy may also be useful in some patients for identifying other causes of lung disease, such as chronic bronchitis.

Typical lesions identified by computed tomography are often used in making a presumptive diagnosis of idiopathic pulmonary fibrosis in people. Similar lesions may be seen in some dogs with the disease (Johnson et al., 2005). Results of computed tomography in cats have not been reported.

A definitive diagnosis of pulmonary fibrosis requires a lung biopsy obtained by thoracotomy or thoracoscopy. The expense and invasiveness of biopsy preclude its use in some



#### FIG 22-4

Lateral thoracic radiograph from a cat with idiopathic pulmonary fibrosis showing a diffuse interstitial pattern with patchy areas of alveolar disease in the caudal lung lobes. Pericardial and mediastinal fat are also seen. Radiographic abnormalities in cats with fibrosis are quite variable, including the range of interstitial, bronchial, alveolar, or mixed patterns.

patients. Furthermore, the lack of specific treatment recommendations for pulmonary fibrosis is a deterrent. However, biopsy should be considered in patients that are stable and whose owners have sufficient resources. The less invasive tests cannot completely rule out the existence of a different, directly treatable disease (e.g., atypical bacterial infection, fungal disease, parasitism), and more aggressive treatment for pulmonary fibrosis could be recommended with histologic confirmation of the diagnosis.

#### **Treatment**

Even in people, large, well-controlled studies have not been performed to determine the ideal treatment strategy for idiopathic pulmonary fibrosis (Hoyles et al., 2006). Most individuals are treated with prednisone at low dosages and azathioprine. Cyclophosphamide is used routinely by some physicians and only during exacerbations by others. Corticosteroids alone are not considered to be effective. Many other drugs, including colchicine and penicillamine, have been tried or investigated, but thus far none have been proved convincingly effective. Survival rates 5 years after the diagnosis remain only 20% to 30% with treatment.

Most dogs and cats have been treated with corticosteroids and bronchodilators. Theophylline derivatives have the theoretical potential to provide some benefit through potentiation of steroid activity. On the basis of clinical experience with people, the addition of azathioprine or cyclophosphamide may be of benefit. Animals with severe pulmonary hypertension may benefit from treatment of this complication (p. 316).

#### **Prognosis**

The prognosis for idiopathic pulmonary fibrosis in dogs and cats is poor, with relentless progression of disease expected.

Nevertheless, individual patients, particularly dogs, can survive for longer than a year. The mean survival time in dogs in one study was 18 months from the onset of signs, with survival up to 3 years (Corcoran et al., 1999). The prognosis in cats is poorer. Of 23 cats, 14 died or were euthanized within weeks of the onset of signs and only 7 of 23 survived longer than 1 year (Cohn et al., 2004).

#### **PULMONARY NEOPLASIA**

Primary pulmonary tumors, metastatic neoplasia, and multicentric neoplasia can all involve the lungs. Most primary pulmonary tumors are malignant. Carcinomas predominate and include adenocarcinoma, bronchoalveolar carcinoma, and squamous cell carcinoma. Sarcomas and benign tumors are much less common. Small cell carcinoma, or oat cell tumor, which occurs frequently in people, is rare in dogs and cats.

The lungs are a common site for the metastasis of malignant neoplasia from other sites in the body and even from primary pulmonary tumors. Neoplastic cells can be carried in the bloodstream and trapped in the lungs, where there is low blood flow and an extensive capillary network. Lymphatic spread or local invasion can also occur.

Multicentric tumors can involve the lungs. Such tumors include lymphoma, malignant histiocytosis, and mastocytoma. An unusual lymphoproliferative tumor limited to involvement of the lung is *lymphomatoid granulomatosis*. This neoplasm is characterized by the infiltration of pleomorphic lymphoreticular and plasmacytoid cells around and into blood vessels, with accompanying eosinophils, neutrophils, lymphocytes, and plasma cells.

Multiple tumors of different origins can occur in the same animal. In other words, the presence of a neoplasm in one site of the body does not necessarily imply that the same tumor is also present in the lungs.

#### **Clinical Features**

Neoplasms are most common in older animals but also occur in young adult animals. Tumors involving the lungs can produce a wide spectrum of clinical signs. These signs are usually chronic and slowly progressive, but peracute manifestations such as pneumothorax or hemorrhage can also occur.

Most signs reflect respiratory tract involvement. Infiltration of the lung by the tumor can cause interference with oxygenation, leading to increased respiratory efforts and exercise intolerance. Mass lesions can compress airways, provoking cough and obstructing ventilation. Erosion through vessels can result in pulmonary hemorrhage. The blood loss can be sudden, resulting in acute hypovolemia and anemia in addition to respiratory compromise. Edema, nonseptic inflammation, or bacterial infection can occur secondary to the tumor. Erosion through the airways can result in pneumothorax. Pleural effusion of nearly any character can form.

In rare cases, the caudal or cranial venae cavae are obstructed, resulting in the development of ascites or head and neck edema, respectively.

Nonspecific signs in dogs and cats with pulmonary neoplasms include weight loss, anorexia, depression, and fever. Gastrointestinal signs may be the primary complaint. Vomiting and regurgitation may be the presenting signs in cats in particular. Lameness may be the presenting sign in patients with hypertrophic osteopathy secondary to thoracic mass lesions and in cats with metastasis of carcinoma to their digits.

Some animals with lung neoplasia have no clinical signs at all, and the tumor is discovered as an incidental finding on thoracic radiographs or at postmortem examination. Animals with metastatic or multicentric lung neoplasia can be seen because of signs of tumor involvement in another organ.

Lung sounds may be normal, decreased, or increased. They are decreased over all lung fields in animals with pneumothorax or pleural effusion. Localized decreased or increased lung sounds can be heard over regions that are consolidated. In a few patients, crackles and wheezes can be auscultated. There may be evidence of other organ involvement or hypertrophic osteopathy.

#### **Diagnosis**

Neoplasia is definitively diagnosed through the histologic or cytologic identification of criteria of malignancy in populations of cells in pulmonary specimens (Fig. 22-5). Thoracic radiographs are commonly evaluated initially, and findings can support a tentative diagnosis of neoplasia. Radiographs can also be used to identify the location of disease, and this information helps the clinician select the most appropriate technique for specimen collection.

Good-quality radiographs, including both left and right lateral projections, should be evaluated. Primary pulmonary tumors can cause localized mass lesions (see Figs. 20-7 and 20-10) or the consolidation of an entire lobe (see Fig. 20-9, A). Tumor margins are often distinct but can be ill-defined as a result of associated inflammation and edema. Cavitation may be evident. Metastatic or multicentric disease results in a diffuse reticular, nodular, or reticulonodular interstitial pattern (see Fig. 20-8). In cats primary lung tumors often have a diffuse distribution by the time of presentation, and the radiographic pattern may be suggestive of bronchitis, edema, or pneumonia.

Pulmonary neoplasia is occasionally associated with hemorrhage, edema, inflammation, infection, or airway occlusion that can contribute to the formation of alveolar patterns and consolidation. Lymphadenopathy, pleural effusion, or pneumothorax can also be identified by radiography in some patients with neoplasia.

Nonneoplastic disease, including fungal infection, lung parasites, the aspiration of mineral oil, eosinophilic granulomatosis, atypical bacterial infections, and inactive lesions from previous disease, can produce similar radiographic abnormalities. Pulmonary specimens must be evaluated to

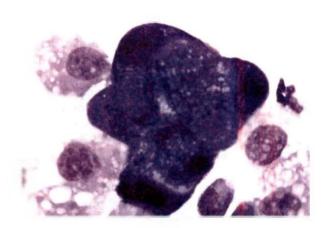


FIG 22-5

Bronchoalveolar lavage fluid from the dog whose lateral thoracic radiograph showing a severe, unstructured interstitial pattern is depicted in Fig. 20-8. Many clumps of deeply staining epithelial cells showing marked criteria of malignancy were seen. One such clump is shown here. A diagnosis of carcinoma was made. Note that a cytologic diagnosis of carcinoma should not be made if there is concurrent inflammation. The surrounding lighter-staining cells are alveolar macrophages, the normal predominant cell type in bronchoalveolar lavage fluid.

establish a diagnosis. Tracheal wash fluid cytology rarely results in a definitive diagnosis. It is generally necessary to evaluate lung aspirates, bronchoalveolar lavage fluid, or lung biopsy specimens.

It may be appropriate to delay the collection of pulmonary specimens in asymptomatic animals with multifocal disease or animals with significant unrelated problems. Rather, radiographs are obtained again in 4 to 6 weeks to document the progression of lesions. Such delay is never recommended in dogs or cats with potentially resectable disease.

The confirmation of malignant neoplasia in other organs in conjunction with typical thoracic radiographic abnormalities is often adequate for making a presumptive diagnosis of pulmonary metastases. Overinterpretation of subtle radiographic lesions should be avoided. Conversely, the absence of radiographic changes does not eliminate the possibility of metastatic disease.

Evaluation of the thorax by computed tomography should be considered in patients with known or suspected neoplasia. Computed tomography is much more sensitive than thoracic radiography in the detection of metastatic disease (see Chapter 20). In patients with localized disease for whom surgical excision is being planned, computed tomography provides more detailed anatomic information regarding the involvement of adjacent structures and is also more accurate in identifying involvement of tracheobronchial lymph nodes, compared with radiography (Paoloni et al., 2006).

#### **Treatment**

Solitary pulmonary tumors are treated by surgical resection. To obtain clear margins, usually the entire lung lobe that is involved must be excised. Lymph node biopsy specimens, as well as biopsy specimens from any grossly abnormal lung, are obtained for histologic analysis.

In animals with a large mass lesion, respiratory signs may abate after excision, even if metastatic lesions are present throughout the lungs. If the lesions cannot be removed surgically, chemotherapy can be attempted (see Chapter 77). No protocol is uniformly effective for the treatment of primary lung tumors.

Metastatic neoplasms of the lungs are treated with chemotherapy. In most animals the initial protocol is determined by the expected sensitivity of the primary tumor. Unfortunately, metastatic neoplasms do not always have the same response to specific agents as the primary tumor.

Multicentric tumors are treated with standard chemotherapeutic protocols, regardless of whether the lungs are involved. Multicentric tumors are discussed in Chapter 79. Lymphomatoid granulomatosis is treated with chemotherapy designed to treat lymphoma (see Chapter 80).

#### **Prognosis**

The prognosis for animals with benign neoplasms is excellent, but these tumors are uncommon. The prognosis for animals with malignant neoplasia is potentially related to several variables, which include tumor histology, presence of regional lymph node involvement, and presence of clinical signs. Survival times of several years are possible after surgical excision. Ogilvie et al. (1989) reported that of 76 dogs with primary pulmonary adenocarcinoma, surgical excision resulted in remission (i.e., elimination of all macroscopic evidence of tumor) in 55 dogs. The median survival time of dogs that went into remission was 330 days, whereas the survival time in dogs that did not achieve remission was 28 days. At the completion of the study, 10 dogs remained alive. McNiel et al. (1997) found that the histologic score of the tumor, presence of clinical signs, and regional lymph node metastases were significantly associated with the prognosis in 67 dogs with primary lung tumors. Median survival times for dogs with and without clinical signs were 240 and 545 days, respectively. Median survival times for dogs with and without lymph node involvement were 26 and 452 days, respectively. Median survival times for dogs with papillary carcinoma were 495 days, compared with 44 days for dogs with other histologic tumor types. Survival times ranged from 0 to 1437 days. A report of 21 cats with primary lung tumors found a median survival time of 115 days after surgery (Hahn et al., 1998). Cats with moderately differentiated tumors had a median survival time of 698 days (range of 13 to 1526 days), whereas cats with poorly differentiated tumors had a median survival time of 75 days (range of 13 to 634 days). The prognosis for animals with multicentric neoplasms is not known to depend on the presence or absence of pulmonary involvement.

#### PULMONARY HYPERTENSION

#### Etiology

Increased pulmonary arterial pressure (i.e., pulmonary systolic pressure >30 mmHg) is called *pulmonary hypertension*. The diagnosis is most accurately made by direct pressure measurements via cardiac catheterization, a procedure rarely performed in dogs or cats. An estimation of pulmonary artery pressure can be made by Doppler echocardiography in patients with pulmonary or tricuspid valvular insufficiency (see Chapter 6). The increasing availability of this technology has increased awareness of the existence of pulmonary hypertension in veterinary medicine. Causes of pulmonary hypertension include obstruction to venous drainage as can occur with heart disease (see Chapter 6), increased pulmonary blood flow caused by congenital heart lesions (see Chapter 5), and increased pulmonary vascular resistance. Genetic factors may influence the occurrence of pulmonary hypertension in some individuals but not in others with the same disease. When no underlying disease can be identified to explain the hypertension, a clinical diagnosis of primary (idiopathic) pulmonary hypertension is made.

Pulmonary vascular resistance can be increased as a result of pulmonary thromboembolism (see p. 317) or heartworm disease (see Chapter 10). Vascular resistance can also be increased as a complication of chronic pulmonary parenchymal disease, such as canine chronic bronchitis (see p. 287) and idiopathic pulmonary fibrosis (see p. 312). A simplistic explanation for increased vascular resistance as a complication of pulmonary disease is the adaptive response of the lung to improve the matching of ventilation and perfusion  $(\dot{V}/\dot{Q})$  through hypoxic vasoconstriction. However, in people other factors are thought to contribute significantly to the development of hypertension associated with pulmonary disease, including endothelial dysfunction, vascular remodeling, and possibly thrombosis in situ.

#### Clinical Features and Diagnosis

Pulmonary hypertension is diagnosed more commonly in dogs than cats. Clinical signs include those of progressive hypoxemia and can be difficult to distinguish from any underlying cardiac or pulmonary disease. Signs of pulmonary hypertension include exercise intolerance, weakness, syncope, and respiratory distress. Physical examination may reveal a loud split S2 heart sound (see Chapter 6). Radiographic evidence of pulmonary hypertension may be present in severely affected patients and includes pulmonary artery enlargement and right-sided cardiomegaly. Radiographs are evaluated closely for underlying cardiopulmonary disease. The diagnosis of pulmonary hypertension is most often made through Doppler echocardiography. Use of this modality to estimate pulmonary artery pressure requires the presence of pulmonary or tricuspid regurgitation and a highly skilled echocardiographer.

#### **Treatment**

Pulmonary hypertension is best treated by identifying and aggressively managing the underlying disease process. In people pulmonary hypertension associated with chronic bronchitis is usually mild and not directly treated. Longterm oxygen therapy is often provided, but this treatment is rarely practical for veterinary patients. Direct treatment can be attempted in patients showing clinical signs of pulmonary hypertension if no underlying disease is identified or management fails to improve pulmonary arterial pressures. Unfortunately, little is known about the treatment of pulmonary hypertension in animals, and adverse consequences can occur through worsening of V/Q matching or other drugrelated side effects. Therefore careful monitoring of clinical signs and pulmonary artery pressures is indicated. The drug most commonly used to treat pulmonary hypertension in dogs is sildenafil citrate (Viagra, Pfizer), a phosphodiesterase V inhibitor that causes vasodilation through a nitric oxide pathway. Dosage and toxicity studies have not been published, but a dosage range between 0.5 and 2.7 mg/kg (median 1.9 mg/kg) orally every 8 to 24 hours has been reported (Bach et al., 2006). A dosage of 0.5 mg/kg orally every 12 hours can be used initially and increased to effect. Long-term anticoagulation with warfarin or heparin is often prescribed for people with primary pulmonary hypertension to prevent small thrombi formation. Its potential benefits for veterinary patients are not known (see the next section, on the treatment of pulmonary thromboembolism).

#### Prognosis

The prognosis for pulmonary hypertension is presumably influenced by the severity of hypertension, presence of clinical signs, and any underlying disease.

#### **PULMONARY THROMBOEMBOLISM**

The extensive low-pressure vascular system of the lungs is a common site for emboli to lodge. It is the first vascular bed through which thrombi from the systemic venous network or right ventricle pass. The respiratory signs can be profound and even fatal in dogs and cats. Hemorrhage, edema, and bronchoconstriction, in addition to the decreased blood flow, can contribute to the respiratory compromise. The attendant increased vascular resistance secondary to the physical obstruction by emboli and vasoconstriction results in pulmonary hypertension, which can ultimately lead to the development of right-sided heart failure.

Thromboemboli generally form as a result of disease in organs other than the lungs, and a search for the underlying cause of clot formation is therefore essential. Abnormalities predisposing to clot formation include venous stasis, turbulent blood flow, endothelial damage, and hypercoagulation. In addition to emboli originating from thrombi, emboli can consist of bacteria, parasites, neoplasia, or fat. Conditions that have been associated with the development of pulmo-



BOX 22-3

Abnormalities Potentially Associated with Pulmonary Thromboembolism\*

Surgery
Severe trauma
Hyperadrenocorticism, Chapter 53
Immune-mediated hemolytic anemia
Hyperlipidemia, Chapter 54
Glomerulopathies, Chapter 43
Dirofilariasis and adulticide therapy, Chapter 10
Cardiomyopathy, Chapters 7 and 8
Endocarditis, Chapter 6
Pancreatitis, Chapter 40
Disseminated intravascular coagulation, Chapter 87
Hyperviscosity syndromes
Neoplasia

nary emboli, and the pages where they are discussed, are listed in Box 22-3. The remainder of this discussion is limited to pulmonary thromboembolism (PTE).

#### **Clinical Features**

In many instances, the predominant presenting sign of animals with PTE is peracute respiratory distress. Cardiovascular shock and sudden death can occur. As awareness of PTE has increased, the diagnosis is being made with greater frequency in patients with milder and more chronic signs of tachypnea or increased respiratory efforts. Historic or physical examination findings related to a potential underlying disease increase the index of suspicion for a diagnosis of PTE. A loud or split-second heart sound (see Chapter 1) may be heard on auscultation and is indicative of pulmonary hypertension. Crackles or wheezes are heard in occasional cases.

#### **Diagnosis**

Routine diagnostic methods do not provide information that can be used to make a definitive diagnosis of PTE. A high index of suspicion must be maintained because this disease is frequently overlooked. The diagnosis is suspected on the basis of clinical signs, thoracic radiography, arterial blood gas analysis, echocardiography, and clinicopathologic data. A definitive diagnosis requires spiral (helical) computed tomography, angiography, or nuclear perfusion scanning, but spiral (helical) computed tomography is becoming the routine modality for diagnosis in people.

PTE is suspected in dogs and cats with severe dyspnea of acute onset, particularly if there are minimal or no radiographic signs of respiratory disease. In many cases of PTE the lungs appear normal on thoracic radiographs in spite of the severe lower respiratory tract signs. When radiographic lesions occur, the caudal lobes are most often involved. Blunted pulmonary arteries, in some cases ending with focal

<sup>\*</sup> Discussions of these abnormalities can be found in the given chapters.

or wedge-shaped areas of interstitial or alveolar opacities resulting from the extravasation of blood or edema, may be present. Areas of lung without a blood supply can appear hyperlucent. Diffuse interstitial and alveolar opacities and right-sided heart enlargement can occur. Pleural effusion is present in some cases and is usually mild. Echocardiography may show secondary changes (e.g., right ventricular enlargement, increased pulmonary artery pressures), underlying disease (e.g., heartworm disease, primary cardiac disease), or residual thrombi.

Arterial blood gas analysis can show hypoxemia to be mild or profound. Tachypnea leads to hypoxepnia, except in severe cases, and the abnormal alveolar-arterial oxygen gradient (*A-a* gradient) supports the presence of a ventilation-perfusion disorder (see Chapter 20). A poor response to oxygen supplementation is supportive of a diagnosis of PTE.

Clinicopathologic evidence of a disease known to predispose animals to thromboemboli further heightens suspicion for this disorder. Unfortunately, measurements of clotting parameters are not helpful in making the diagnosis. In people measurement of circulating D-dimers (a degradation product of cross-linked fibrin) is used as an indicator of the likelihood of PTE. It is not considered a specific test, so its primary value has been in the elimination of PTE from the differential diagnoses. However, even a negative result can be misleading in certain disease states and in the presence of small subsegmental emboli.

Measurement of D-dimer concentrations is available for dogs through commercial laboratories. A study of 30 healthy dogs, 67 clinically ill dogs without evidence of thromboembolic disease, and 20 with thromboembolic disease provides some guidance for interpretation of results (Nelson et al., 2003). A D-dimer concentration of >500 ng/ml was able to predict the diagnosis of thromboembolic disease with 100% sensitivity but with a specificity of only 70% (i.e., having 30% false-positive results). A D-dimer concentration of >1000 ng/ml decreased the sensitivity of the result to 94% but increased the specificity of the result to 80%. A D-dimer concentration >2000 ng/ml decreased the sensitivity of the result to 36% but increased the specificity to 98.5%. Thus the degree of elevation in D-dimer concentration must be considered in conjunction with other clinical information.

Spiral (helical) computed tomography is commonly used in people to confirm a diagnosis of PTE and is being used increasingly to confirm the diagnosis in veterinary medicine. One limitation of thoracic computed tomography in dogs and especially cats is patient size. In addition, veterinary patients will not hold their breath. Patients must be anesthetized and positive pressure ventilation applied during scanning for maximal resolution. A high quality computed tomography scanner and an experienced radiologist are required for accurate interpretation.

Angiography can provide a definitive diagnosis of PTE. Sudden pruning of pulmonary arteries or intravascular filling defects and extravasation of dye are characteristic

findings. However, these changes may be apparent for only a few days after the event, so this test must be done early in the disease. Nuclear scans can provide evidence of PTE with minimal risk to the animal. Unfortunately, this technology is for the most part available only at academic institutions.

Pulmonary specimens for histopathologic evaluation are rarely collected, except at necropsy. However, evidence of embolism is not always found at necropsy because clots may dissolve rapidly after death. Therefore such tissue should be collected and preserved immediately after death. The extensive vascular network makes it impossible to evaluate all possible sites of embolism, and the characteristic lesions may also be missed.

#### **Treatment**

Shock therapy may be needed for patients in severe distress, including high doses of rapid-acting glucocorticoids (e.g., prednisolone sodium succinate, up to 10 mg/kg intravenously). Animals should also receive immediate oxygen therapy (see Chapter 27).

Animals with suspected hypercoagulability are likely to benefit from anticoagulant therapy. Large-scale clinical studies of the response of dogs or cats with PTE to anticoagulant therapy have not been published. Anticoagulant therapy is administered only to animals in which the diagnosis is highly probable. Dogs with heartworm disease suffering from postadulticide therapy reactions usually are not treated with anticoagulants (see Chapter 10). Potential surgical candidates should be treated with great caution. Clotting times must be monitored frequently to minimize the risk of severe hemorrhage. General guidelines for anticoagulant therapy are provided here. However, more complete descriptions of anticoagulant therapy are available in the literature, and a current pharmacology text should be consulted before anticoagulants are used.

Initially, heparin (200 to 300 U/kg subcutaneously q8h) is administered for anticoagulant therapy. The goal of heparin therapy is to maintain the partial thromboplastin time (PTT) at 1.5 to 2.5 times normal, which corresponds to approximately a 1.2 to 1.4 times increase above the normal activated clotting time (ACT). Clotting times are evaluated before and 2 hours after the administration of heparin, and the dosage is adjusted on the basis of the results.

Hemorrhage is a potential complication of heparin therapy. Protamine sulfate is a heparin antagonist that can be administered if bleeding is not adequately controlled after heparin treatment is discontinued. Some clinicians advocate gradually tapering the dosage of heparin over several days when discontinuing treatment to avoid rebound hypercoagulation.

Heparin can be administered by the owner at home, but long-term anticoagulation is usually maintained with oral warfarin. Animals receiving warfarin therapy require frequent monitoring, and dosage adjustments are common. The potential for drug interactions with all concurrent medications being administered must be considered. An initial dosage of 0.1 to 0.2 mg/kg by mouth every 24 hours is pre-

scribed for dogs, and a total of 0.5 mg every 24 hours is prescribed for most cats. The goal of therapy is to maintain a prothrombin time (PT) of 1.5 to 2 times normal or an international normalization ratio (INR) of 2.0 to 3.0. It appears that it is safer to use the INR than the PT for monitoring anticoagulation. The INR is calculated from the measured PT and corrects for the variable strength of the thromboplastin reagent used in the assay. The INR or the formula to calculate it can be obtained from the commercial laboratory or the supplier of in-office test kits. Heparin therapy can be discontinued once the desired prolongation has been reached. It may be possible to decrease the frequency of administration of oral warfarin to every 48 hours after several days of treatment.

Until the PT has stabilized, which takes a minimum of 5 days, clotting times are assessed daily. Subsequent examination of the animal and evaluation of clotting times are performed at least every 5 days, with the interval gradually increasing to every 4 to 6 weeks if consistent and favorable results are obtained.

Excessive hemorrhage is the primary complication of warfarin therapy. Plasma or vitamin K<sub>1</sub> (2 to 5 mg/kg q24h) can be used to treat uncontrollable hemorrhage. However, if vitamin K is used, further attempts at anticoagulation using warfarin cannot be made for several weeks.

The use of fibrinolytic agents for the treatment of PTE in animals has not been well established. Recombinant tissue plasminogen activator has shown promise because it acts locally at sites of fibrin deposition.

Because of the serious problems and limitations associated with anticoagulant therapy, eliminating the predisposing problem must be a major priority.

#### **Prevention**

No methods of preventing PTE in at-risk patients have been objectively studied in veterinary medicine. Treatments that have potential benefit include the long-term administration of low molecular weight heparin, aspirin, or clopidagrel. Aspirin for the prevention of PTE remains controversial because aspirin-induced alterations in local prostaglandin and leukotriene metabolism may be detrimental.

#### **Prognosis**

The prognosis depends on the severity of the respiratory signs and the ability to eliminate the underlying process. In general, a guarded prognosis is warranted.

#### **PULMONARY EDEMA**

#### **Etiology**

The same general mechanisms that cause edema elsewhere in the body cause edema in the pulmonary parenchyma. Major mechanisms are decreased plasma oncotic pressure, vascular overload, lymphatic obstruction, and increased vascular permeability. The disorders that can produce these problems are listed in Box 22-4.



#### Possible Causes of Pulmonary Edema

#### **Decreased Plasma Oncotic Pressure**

Hypoalbuminemia
Gastrointestinal loss
Glomerulopathy
Liver disease
latrogenic overhydration
Starvation

#### Vascular Overload

Cardiogenic Left-sided heart failure Left-to-right shunts Overhydration

#### **Lymphatic Obstruction (Rare)**

Neoplasia

#### **Increased Vascular Permeability**

Inhaled toxins
Smoke inhalation
Gastric acid aspiration
Oxygen toxicity
Drugs or toxins
Snake venom
Cisplatin in cats

Electrocution

Trauma Pulmonary

Multisystemic

Sepsis

Pancreatitis

Uremia

Disseminated intravascular coagulation Inflammation (infectious or noninfectious)\*

#### Miscellaneous Causes

Thromboembolism
Upper airway obstruction
Near-drowning
Neurogenic edema
Seizures
Head trauma

The fluid initially accumulates in the interstitium. However, because the interstitium is a small compartment, the alveoli are soon involved. When profound fluid accumulation occurs, even the airways become filled. Respiratory function is further affected as a result of the atelectasis and decreased compliance caused by compression of the alveoli and decreased concentrations of surfactant. Airway resistance increases as a result of the luminal narrowing of small bronchioles. Hypoxemia results from ventilation-perfusion abnormalities.

<sup>\*</sup>Inflammation is usually the prominent clinical abnormality, not edema.

#### **Clinical Features**

Animals with pulmonary edema are seen because of cough, tachypnea, respiratory distress, or signs of the inciting disease. Crackles are heard on auscultation, except in animals with mild or early disease. Blood-tinged froth may appear in the trachea, pharynx, or nares immediately preceding death from pulmonary edema. Respiratory signs can be peracute, as in acute respiratory distress syndrome (ARDS), or subacute, as in hypoalbuminemia. However, a prolonged history of respiratory signs (e.g., months) is not consistent with a diagnosis of edema. The list of differential diagnoses in Box 22-4 can often be greatly narrowed by obtaining a thorough history and performing a thorough physical examination.

#### Diagnosis

Pulmonary edema in most dogs and cats is based on typical radiographic changes in the lungs in conjunction with clinical evidence (from the history, physical examination, radiography, echocardiography, and serum biochemical analysis [particularly albumin concentration]) of a disease associated with pulmonary edema.

Early pulmonary edema assumes an interstitial pattern on radiographs, which progresses to become an alveolar pattern. In dogs edema caused by heart failure is generally more severe in the hilar region. In cats the increased opacities are more often patchy and unpredictable in their distribution. Edema resulting from increased vascular permeability tends to be most severe in the dorsocaudal lung regions.

Radiographs should be carefully examined for signs of heart disease, venous congestion, PTE, pleural effusion, and mass lesions. Echocardiography is helpful in identifying primary cardiac disease if the clinical signs and radiographic findings are ambiguous.

Decreased oncotic pressure can be identified by the serum albumin concentration. Concentrations less than 1 g/dl are usually required before decreased oncotic pressure is considered to be the sole cause of the pulmonary edema. Pulmonary edema resulting purely from hypoalbuminemia is probably rare. In many animals volume overload or vasculitis is a contributing factor. Plasma protein quantitation using a refractometer can indirectly assess albumin concentration in emergency situations.

Vascular permeability edema, or noncardiogenic pulmonary edema, can result in the full range of compromise, from minimal clinical signs that spontaneously resolve to the frequently fatal, fulminant process of ARDS. ARDS, or "shock lung," describes a syndrome of acute, rapidly progressive pulmonary edema. In a review of 19 dogs with ARDS by Parent et al. (1996), the time of onset of dyspnea ranged from 0.5 to 48 hours (mean 4.5 hours) before admission, and the duration of dyspnea before death in dogs not mechanically ventilated ranged from 8 to 76 hours (mean 16 hours).

Pulmonary specimens from patients with vascular permeability edema are not cytologically unique, showing a predominantly neutrophilic response. Arterial blood gas analysis and pulse oximetry in dogs and cats with pulmonary edema are useful in selecting and monitoring therapy. Hypoxemia is present, usually in conjunction with hypoxapnia and a widened *A-a* gradient.

#### **Treatment**

It is easier for the body to prevent edema fluid from forming than it is to mobilize existing fluid. The initial management of pulmonary edema should be aggressive. Once the edema has resolved, the body's own compensatory mechanisms become more effective and the intensity of therapeutic interventions can often be decreased.

All animals with pulmonary edema are treated with cage rest and minimal stress. Dogs and cats with significant hypoxemia should receive oxygen therapy (see Chapter 27). Positive-pressure ventilation is required in severe cases. Methylxanthine bronchodilators (see pp. 290 and 296) may also be beneficial in some patients. They are mild diuretics and also decrease bronchospasms and possibly respiratory muscle fatigue. However, in some patients bronchodilators exacerbate ventilation:perfusion (V/Q) mismatching. The patient's response to bronchodilators should be carefully observed.

Furosemide is indicated for the treatment of most forms of edema but is not used in hypovolemic animals. Animals with hypovolemia actually require conservative fluid supplementation. If this is necessary to maintain the vascular volume in animals with cardiac impairment or decreased oncotic pressure, then positive inotropic agents or plasma infusions, respectively, are necessary.

Edema caused by hypoalbuminemia is treated with plasma or colloid infusions. However, it is not necessary for the plasma protein concentrations to reach normal levels for edema to decrease. Furosemide can be administered to more quickly mobilize the fluid from the lungs, but clinical dehydration and hypovolemia must be prevented. Diagnostic and therapeutic efforts are directed at the underlying disease.

The treatment of cardiogenic edema is discussed in Chapter 3.

Overhydration is treated by the discontinuation of fluid therapy. Furosemide is administered if respiratory compromise is present. If excessive volumes of fluid were not administered inadvertently, causes of fluid intolerance, such as oliguric renal failure, heart failure, and increased vascular permeability, must be sought.

Edema caused by increased vascular permeability is difficult to treat. In some cases, pulmonary compromise is mild and the edema transient. Routine supportive care with oxygen supplementation may be sufficient, but mechanical ventilation is often required. Any active underlying problem should be identified and corrected.

ARDS responds poorly to management. Ventilator therapy with positive end-expiratory pressure is indicated, and even with such aggressive support the mortality rate is high. Furosemide is generally ineffective in treating edema caused by increased vascular permeability, but because of limitations in our diagnostic capabilities, it is reasonable to include this

drug in the initial management of these patients. Glucocorticoids are of no clear benefit in these patients, but they are frequently given to animals with moderate to severe signs. Many novel therapics for ARDS have been studied in people, although to date none has been shown to be consistently effective in improving outcome. Studies are ongoing. Examples of such therapies include endotoxin blockers, inhibitors of specific inflammatory mediators, inhaled nitrous oxide, antioxidant drugs, and surfactant replacement.

#### **Prognosis**

The prognosis for an animal with pulmonary edema depends on the severity of the edema and the ability to eliminate or control the underlying problem. Aggressive management early in the course of edema formation improves the prognosis for an animal with any given disease. Animals with ARDS have a guarded to grave prognosis.

#### Suggested Readings

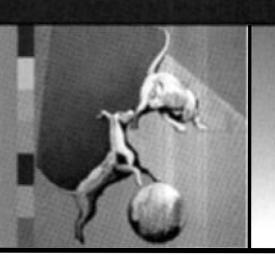
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### CHAPTER

### Clinical Manifestations of the Pleural Cavity and Mediastinal Disease



#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
PLEURAL EFFUSION: FLUID CLASSIFICATION AND
DIAGNOSTIC APPROACH

Transudates and Modified Transudates
Septic and Nonseptic Exudates
Chylous Effusions
Hemorrhagic Effusions
Effusions Caused by Neoplasia
PNEUMOTHORAX
MEDIASTINAL MASSES
PNEUMOMEDIASTINUM

#### GENERAL CONSIDERATIONS

Common abnormalities of the pleural cavity in the dog and cat include the accumulation of fluid (pleural effusion) or air (pneumothorax) in the pleural space. Mediastinal masses and pneumomediastinum are also discussed in this chapter. Respiratory signs caused by pleural disease result from interference with normal expansion of the lungs. Exercise intolerance is an early sign; overt respiratory distress ultimately occurs. Physical examination findings that assist in localizing the cause of respiratory compromise to the pleural space include increased respiratory rate and decreased lung sounds on auscultation (see Chapter 26). With increasing compromise, increased abdominal excursions during breathing may be seen. Breathing effort may be increased during inspiration relative to expiration, but this finding is not always obvious. In cats with mediastinal masses, decreased compressibility of the anterior thorax may be palpable. Thoracic radiography, thoracocentesis, or both are performed to confirm the presence of pleural space disease.

Pulmonary thromboembolism (PTE) can cause a pleural effusion. The effusion is generally mild and may be an exudate or a modified transudate. PTE should be considered as a diagnosis particularly in patients whose respiratory

efforts seem in excess of the volume of effusion (see Chapter 22).

### PLEURAL EFFUSION: FLUID CLASSIFICATION AND DIAGNOSTIC APPROACH

The presence of pleural effusion in a dog or cat is usually confirmed by thoracic radiography or thoracocentesis (see Chapter 24). In animals presented in respiratory distress with suspected pleural effusion, thoracocentesis is performed immediately to stabilize the animal's condition before radiographs are taken. Although thoracocentesis is more invasive than radiography, the potential therapeutic benefit of the procedure far outweighs the small risk of complications. Animals in stable condition at presentation can be evaluated initially with thoracic radiographs to confirm the presence and location of fluid before thoracocentesis is performed.

Ultrasonography is a valuable tool for the evaluation of patients with pleural effusion. If equipment is available on site, animals in critical condition can be examined ultrasonographically with minimal stress to confirm both the presence of fluid and direct needle placement for thoracocentesis. Ultrasonography is also useful in evaluating the thorax for the presence of mass lesions, hernias, and primary cardiac or pericardial disease. Because sound waves cannot pass through aerated lungs, any masses must be adjacent to the chest wall, heart, or diaphragm to be detected by ultrasound. The presence of pleural fluid facilitates the ultrasonographic evaluation of the chest. If the patient is stable, it is preferable to evaluate the thorax ultrasonographically before removing the pleural fluid.

Thoracic radiographs should be taken again after as much fluid or air as possible has been removed from the pleural space and the lungs have had time to reexpand. Full expansion of the lungs is required for accurate evaluation of the pulmonary parenchyma. The presence of fluid also obscures visibility of heart size and shape and mass lesions.

Cytologic analysis of pleural fluid obtained by thoracocentesis is indicated for the diagnostic evaluation of all



**TABLE 23-1** 

Diagnostic Approach in Dogs and Cats with Pleural Effusion Based on Fluid Type

FLUID TYPE	COMMON DISEASE	DIAGNOSTIC TESTS
Pure and modified transudates	Right-sided heart failure	Evaluate pulses, auscultation, ECG, thor rad, echo
	Pericardial disease	See right-sided heart failure
	Hypoalbuminemia (pure transudate)	Serum albumin concentrations
	Neoplasia	Thor rad and US, CT, thoracoscopy, thoracotomy
	Diaphragmatic hernia	Thor rad and US
Nonseptic exudates	Feline infectious peritonitis (FIP)	Pleural fluid cytology is generally sufficient. In questionable cases available tests are many, but none has shown good specificity for diagnosing FIP. Consider systemic evaluation, ophthalmoscopic examination, serum or fluid electrophoresis, coronavirus antibody titer, PCR of tissues or effusion (see Chapter 97)
	Neoplasia	See Neoplasia above
	Diaphragmatic hernia	See Diaphragmatic hernia above
	Lung lobe torsion	Thor rad and US, bronchoscopy, thoracotomy
Septic exudates	Pyothorax	Gram staining, aerobic and anaerobic cultures, serial thor rad
Chylous effusion	Chylothorax	See Box 25-1
Hemorrhagic effusion	Trauma	History
	Bleeding disorder	Systemic examination, coagulation tests (ACT, PT, PTT), platelet count
	Neoplasia	See Neoplasia above
	Lung lobe torsion	See Lung lobe tarsion above

ACT, Activated, clotting time; CT, computed tomography; ECG, electrocardiography; echo, echocardiography; PCR, polymerase chain reaction; PT, prothrombin time; PTT, partial thromboplastin time; thor rad, thoracic radiography; US, ultrasonography.

animals with pleural effusion. Measurement of the protein concentration and total nucleated cell count, as well as the qualitative assessment of individual cells, is essential for accurately classifying the fluid, formulating a diagnostic plan, and initiating appropriate therapy (Table 23-1).

Pleural fluid is classified as a transudate, modified transudate, or exudate on the basis of protein concentration and nucleated cell count. Further classification of fluid may be possible on the basis of other cytologic or biochemical features. Clinically useful fluid categories include septic exudate, chylous effusion, hemorrhagic effusion, and effusion caused by neoplasia. Although various types of fluid have typical gross appearances (Fig. 23-1), reliance on gross appearance alone will lead to the misclassification of fluid and missed diagnoses (through the failure to identify organisms or abnormal cell populations) in some cases. In addition to the inflammatory cell types in each cytologic category described in the subsequent sections, mesothelial cells are generally present and are often reactive.

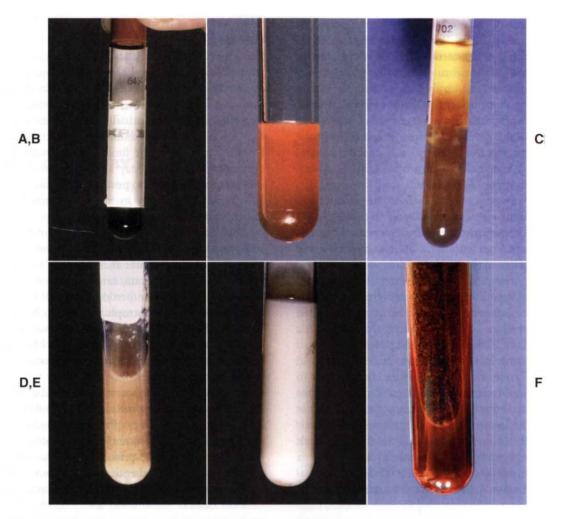
### TRANSUDATES AND MODIFIED TRANSUDATES

Pure transudates are fluids with low protein concentrations of less than 2.5 to 3 g/dl and low nucleated cell counts of less than 500 to 1000/µl. The primary cell types are mononuclear cells, composed of macrophages, lymphocytes, and mesothelial cells. Modified transudates have a slightly higher protein

concentration of up to 3.5 g/dl and nucleated cell counts of up to 5000/µl. The primary cell types include neutrophils as well as mononuclear cells.

Transudates and modified transudates form as a result of increased hydrostatic pressure, decreased plasma oncotic pressure, or a lymphatic obstruction. Increased hydrostatic pressure occurs in association with right-sided congestive heart failure or pericardial disease. Physical examination findings such as abnormal jugular pulses, gallop rhythms, arrhythmias, or murmurs support a diagnosis of heart disease. Heart sounds may be muffled in animals with pericardial effusions. Thoracic radiography (after fluid removal), electrocardiography, and echocardiography are indicated for cardiac evaluation (see Chapter 2).

Decreased plasma oncotic pressure is a result of hypoal-buminemia. Effusions secondary to hypoalbuminemia alone are pure transudates, having very low protein concentrations. Subcutaneous edema may be detected in dependent areas of the body. A decreased production of albumin causes hypoalbuminemia in patients with liver disease, and an increased loss of albumin causes it in patients with glomerulopathies or protein-losing enteropathies. The total plasma protein concentration shown by refractometry during the initial evaluation of the dog or cat can provide an early indication of hypoalbuminemia. Serum biochemical analysis provides an exact measurement of the albumin concentration. In general, albumin concentrations must be



#### FIG 23-1

Characteristic gross appearance of the various types of pleural effusion. Note that cytologic analysis should always be performed to ensure accurate classification of fluid and to avoid missing diagnostic organisms or neoplastic cells. **A,** Transudate. Fluid is nearly clear. **B,** Modified transudate. Fluid is slightly opaque and, in this example, redtinged. **C,** Nonseptic exudate. Fluid is more opaque. The fluid shown is from a cat with feline infectious peritonitis (FIP). FIP fluid is characteristically straw colored with grossly visible fibrin clots. **D,** Septic exudate. Fluid has a purulent appearance, with cellular debris gravitating toward the bottom of the tube. **E,** Chylous effusion. Fluid is milky white. **F,** Hemorrhagic effusion. Hemorrhagic effusions are bright to dark red. In this case, cytologic examination revealed filamentous organisms demonstrating the importance of cytologic analysis.

lower than 1 g/dl before transudation occurs caused only because of hypoalbuminemia.

Lymphatic obstruction can be caused by neoplasia and diaphragmatic hernias. Diaphragmatic hernias should be suspected in any animal with a history of trauma. The trauma may have been recent or may have occurred years ago. Although a modified transudate usually forms as a result of chronic diaphragmatic hernia, an exudative fluid can also be found. Diaphragmatic hernias are identified by radiography or ultrasonography. Occasionally, it is necessary to administer barium orally and perform an upper gastrointestinal series or to intraperitoneally administer water-soluble iodinated contrast media and perform peritoneography to confirm the presence of a diaphragmatic hernia. Normal imaging

findings do not entirely rule out the existence of a tear in the diaphragm, however.

Neoplasia must be considered as a differential diagnosis for patients with any type of effusion, although it is rare for a pure transudate to develop. (See the section on effusions caused by neoplasia for further discussion.)

#### SEPTIC AND NONSEPTIC EXUDATES

Exudates have a high protein concentration (greater than 3 g/dl) compared with that in transudates. Nucleated cell counts are also high (greater than 5000/µl). Cell types in *nonseptic exudates* include neutrophils, macrophages, eosinophils, and lymphocytes. The macrophages and lymphocytes may be activated, and typically the neutrophils are nonde-

generative. There is no evidence of organisms. Differential diagnoses in animals with nonseptic exudates include feline infectious peritonitis (FIP), neoplasia, chronic diaphragmatic hernia, lung lobe torsion, and resolving septic exudates. Prior treatment with antibiotics in animals with a septic effusion can alter the characteristics of the neutrophil population in the fluid, making them appear nondegenerative, and decrease the number of organisms present in the fluid to an undetectable level. Therefore pleural fluid analysis should be performed before treatment is initiated so that bacterial infection is not overlooked.

Cats with FIP can present with fever or chorioretinitis in addition to respiratory signs (see Chapter 97). The pleural fluid protein concentration is often very high in such animals, approaching serum concentrations. It is common to see fibrin strands or clots in the fluid. Careful cytologic evaluation of the fluid is essential to differentiate FIP fluid from exudates caused by pyothorax or malignant lymphoma. The evaluation of animals for diaphragmatic hernia was described in the previous section and is described for neoplasia in a following section (i.e., Effusion Caused by Neoplasia).

Spontaneous lung lobe torsions are most common in dogs with deep, narrow thoracic cavities. In addition to causing an effusion, torsions can be seen in dogs and cats secondary to pleural effusion. Underlying pulmonary disease resulting in lobe atelectasis can also contribute to the development of torsion. Torsion should be considered in animals with a preexisting effusion or pulmonary disease if their condition suddenly deteriorates. The effusion is often a nonseptic exudate, but it may be chylous or hemorrhagic. Signs of lung lobe torsion may be identified through thoracic radiography or ultrasonography (see Chapter 20). Bronchoscopy or thoracotomy is required to verify the condition in some animals.

Septic exudates often have extremely high nucleated cell counts (e.g., 50,000 to more than 100,000/µl), and degenerate neutrophils are the predominant cells. Bacteria can often be observed within neutrophils and macrophages as well as extracellularly (see Fig. 25-1). The fluid may have a foul odor. Septic exudates are diagnostic for pyothorax. Pyothorax can occur spontaneously, secondary to wounds that penetrate into the thoracic cavity through the chest wall or esophagus, secondary to migrating grass awns or other foreign bodies, or as an extension of bacterial pneumonia. Sterile technique should be used during thoracocentesis and chest tube placement in all animals with pleural effusion or pneumothorax to prevent iatrogenic infection.

Gram staining and both aerobic and anaerobic bacterial cultures with antibiotic sensitivity testing should be performed on the fluid. Culture and sensitivity testing provide valuable information that can be used for selecting appropriate antibiotics and monitoring therapy. Mixed bacterial infections are common. However, bacteria do not grow from cultures of all septic exudates, and results are not available for several days. Gram staining provides immediate information that can be used to help select antibiotics and is helpful in cases in which bacteria cannot be grown from the fluid.

#### CHYLOUS EFFUSIONS

Chylous effusion (chylothroax) results from the leakage of fluid from the thoracic duct, which carries lipid-rich lymph from the body. Such leakage can be idiopathic, congenital, or secondary to trauma, neoplasia, cardiac disease, pericardial disease, dirofilariasis, lung lobe torsion, or diaphragmatic hernia. Chyle is usually milky white and turbid (see Fig 23-1, E), largely as a result of chylomicrons that carry fats from the intestines. The fluid is occasionally blood tinged, although this finding may also be an artifact from prior thoracocentesis. It is also possible to obtain clear and colorless fluids, particularly in anorectic animals, but this is uncommon.

Chyle has the cytologic characteristics of a modified transudate or nonseptic exudate with moderate concentrations of protein, usually greater than 2.5 g/dl. The nucleated cell count is low to moderate, ranging from 400 to 10,000/µl. Early in the disease the predominant cell type is the small lymphocyte. A few neutrophils may also be present. With time, nondegenerative neutrophils become more predominant and there are fewer lymphocytes. Macrophages also increase in number with time, and plasma cells may be present.

A diagnosis of chylothorax is confirmed by measuring the concentrations of triglycerides in the pleural fluid and serum. Each specimen should be well mixed by the laboratory before a portion is analyzed because of the tendency for the lipid portion to rise to the surface. The triglyceride content in chyle is high compared with that in serum. Rarely, the test will need to be repeated after a meal in anorectic animals.

Most cases of chylothorax are idiopathic, but this diagnosis can be made only after the other disorders have been ruled out. Treatment is most likely to be successful if an underlying problem is identified and treated directly. (See Chapter 25 for a complete discussion of chylothorax.)

#### **HEMORRHAGIC EFFUSIONS**

Hemorrhagic effusions are grossly red as a result of the large red blood cell content. Hemorrhagic effusions have greater than 3 g/dl of protein and more than 1000 nucleated cells/ $\mu$ l, with a distribution similar to that of peripheral blood. Over time the numbers of neutrophils and macrophages increase. Hemorrhagic effusions (except those obtained immediately after bleeding into the thorax) are readily distinguished from the recovery of peripheral blood through traumatic thoracocentesis by several features: hemorrhagic effusions have erythrophagocytosis and an inflammatory response on cytologic evaluation, hemorrhagic effusions do not clot, and the packed cell volume (PCV) of hemorrhagic effusions is lower than that of peripheral blood.

Hypovolemia and anemia may contribute to the clinical signs of patients with hemothorax (see Chapter 26). Hemothorax can result from trauma, systemic bleeding disorders, neoplasia, and lung lobe torsion. Rarely, septic exudates are grossly hemorrhagic (see Fig 23-1, F) and are distinguished cytologically. Respiratory distress caused by hemothorax may be the only clinical sign in animals with some bleeding

disorders, including rodenticide intoxication. An activated clotting time and platelet count should be performed early in the evaluation of these animals, followed by more specific clotting tests (i.e., prothrombin time and partial thromboplastin time). Hemangiosarcoma of the heart or lungs is a common neoplastic cause of a hemorrhagic effusion, but malignant cells are rarely identified cytologically. Neoplastic effusions are discussed further in the next section.

#### EFFUSIONS CAUSED BY NEOPLASIA

Neoplasia within the thoracic cavity can result in most types of effusion (modified transudates, exudates, chylous effusion, or hemorrhagic effusion). Neoplasms may involve any of the intrathoracic structures, including the lungs, mediastinal tissues, pleura, heart, and lymph nodes. In some cases, neoplastic cells exfoliate from the tumor into the effusion, and an early diagnosis can be made through fluid cytology. This is often possible in patients with mediastinal lymphoma. Unfortunately, other than in cases of lymphoma, it can be difficult or impossible to establish a definitive diagnosis of neoplasia on the basis of cytologic findings in the pleural fluid alone. Inflammation can result in considerable hyperplastic changes of mesothelial cells that are easily confused with neoplastic cells. A cytologic diagnosis of neoplasia other than lymphoma should be made with extreme caution.

In the majority of cases, neoplastic cells are not present in the fluid or a cytologic diagnosis cannot be made. Thoracic radiography and ultrasonography should be performed to evaluate the thorax for evidence of neoplasia (see Chapter 24). Ultrasonography can be used to differentiate localized accumulations of fluid from soft tissue masses. If soft tissue masses are detected, aspirates or biopsy specimens are obtained for cytologic or histopathologic evaluation. A definitive diagnosis cannot be made on the basis of the radiograph findings or ultrasound images alone.

Diffuse neoplastic infiltration of the pleura and some masses cannot be seen with these imaging techniques. Repeated thoracic radiography, computed tomography, thoracoscopy, or surgical exploration may be necessary in such cases.

#### **PNEUMOTHORAX**

Pneumothorax is the accumulation of air in the pleural space. The diagnosis is confirmed by means of thoracic radiography. The pleural cavity is normally under negative pressure, which keeps the lungs expanded in health. However, if an opening forms between the pleural cavity and the atmosphere or the airways of the lungs, air is transferred into the pleural space because of this negative pressure. A tension pneumothorax occurs if a one-way valve is created by tissue at the site of leakage, such that air can enter into the pleural space during inspiration but cannot return to the airways or atmosphere during expiration. Increased intrapleural pressure and resultant respiratory distress occur quickly.

Leaks through the thoracic wall can occur after a traumatic injury or as a result of a faulty pleural drainage system. Air can also enter the thorax during abdominal surgery through a previously undetected diaphragmatic hernia. These causes are readily identified.

Pneumothorax resulting from pulmonary air can occur after blunt trauma to the chest (i.e., traumatic pneumothorax) or as a result of existing pulmonary lesions (i.e., spontaneous pneumothorax). Traumatic pneumothorax occurs frequently, and the history and physical examination findings allow this to be diagnosed. Pulmonary contusions are often present in these animals.

Spontaneous pneumothorax occurs when preexisting pulmonary lesions rupture. Cavitary lung diseases include blebs, bullae, and cysts, which can be congenital or idiopathic or result from prior trauma, chronic airway disease, or *Paragonimus* infection. Necrotic centers can develop in neoplasms, thromboembolized regions, abscesses, and granulomas involving the airways, and these can rupture, allowing air to escape into the pleural space. (See Chapter 20 for further discussion of cavitary lesions, and Chapter 25 for further discussion of spontaneous pneumothorax.)

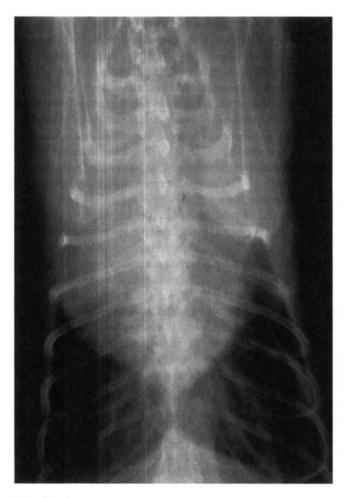
Dogs and cats with pneumothorax and a recent history of trauma are managed conservatively. Cage rest, the removal of accumulating air by periodic thoracocentesis or by chest tube, and radiographic monitoring are indicated. If abnormal radiographic opacities persist without improvement for more than several days in trauma patients, further diagnostic tests should be performed, as described in the section on spontaneous pneumothorax (see Chapter 25).

#### **MEDIASTINAL MASSES**

Mediastinal masses can cause inspiratory distress as a result of displacement of lung tissue by the mass itself or by the secondary pleural effusion that may develop. Additional clinical signs such as coughing, regurgitation, and facial edema may also be present. Neoplasia is the primary differential diagnosis. Lymphoma involving the mediastinum is common, particularly in cats. Other types of neoplasms include thymoma and rarely thyroid carcinoma, parathyroid carcinoma, and chemodectoma. Nonneoplastic mass lesions such as abscesses, granulomas, hematomas, and cysts are other possibilities.

Mediastinal masses in cats can often be palpated during gentle compression of the anterior thorax. Radiographically, mediastinal masses appear as soft tissue opacities in the anterior mediastinum (Fig. 23-2). However, it can be difficult to accurately identify a mediastinal mass if pleural fluid is present. Pleural fluid can both mimic the appearance of a mass and obscure its borders. Ultrasonography done before removal of the pleural fluid is helpful in identifying a mass and determining the extent to which surrounding structures are involved.

Thoracocentesis and fluid analysis should be performed in animals with pleural effusion. Lymphoma can frequently



**FIG 23-2**Ventrodorsal view of the thorax of a cat with an anterior mediastinal mass. Soft tissue opacity fills the anterior mediastinum and obscures the border of the heart.

be diagnosed through the identification of malignant cells in the effusion. Transthoracic fine-needle aspiration or biopsy can be performed to obtain specimens for microscopic evaluation of the mass itself. Aspiration cytology is generally performed initially, followed by biopsy if a cytologic diagnosis is not obtained. Transthoracic biopsy specimens can be obtained relatively safely, particularly if the lesion is solid rather than cystic. Ultrasonography can be helpful in determining the consistency of the mass and can also be used to guide biopsy. Alternatively, sites for sampling can be determined from two radiographic views of the thorax. The dorsal mediastinal area and heart should be avoided when obtaining biopsy samples. A study by Lana et al. (2006) demonstrated the usefulness of flow cytometry of mediastinal mass aspirates in differentiating lymphoma from thymoma in dogs.

Surgical exploration or thoracoscopy may be necessary to biopsy small lesions, cavitary lesions, and lesions adjacent to the heart or main blood vessels. Complete excision of the mass should be attempted at that time, unless lymphoma is diagnosed. (Specific recommendations for the management of dogs and cats with mediastinal neoplasia are given in Chapter 79)

#### **PNEUMOMEDIASTINUM**

Pneumomediastinum is identified radiographically. Subcutaneous emphysema or pneumothorax can occur concurrently or secondarily. Respiratory compromise most often results from pneumothorax. Mediastinal air commonly originates from rupture or tears in the trachea, bronchi, or alveoli. These leaks can occur as a result of bite wounds of the neck or sudden changes in intrathoracic pressure resulting from coughing, blunt trauma, or excessive respiratory efforts against obstructed airways. Potential iatrogenic causes include tracheal washing, tracheostomy, and endotracheal tube placement (usually caused by excessive endotracheal tube cuff pressure). Air can also enter the mediastinum through esophageal tears, generally resulting from foreign bodies.

Strict cage rest is indicated for animals with pneumomediastinum to facilitate natural sealing of the tear. If air continues to accumulate, causing respiratory compromise, bronchoscopy should be performed to identify tracheal or bronchial lacerations that may require surgical repair.

#### **Suggested Readings**

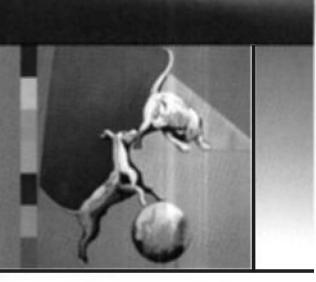
Hardie EM et al: Tracheal rupture in cats: 16 cases (1983-1998), J Am Vet Med Assoc 214:508, 1999.

Lana S et al: Diagnosis of mediastinal masses in dogs by flow cytometry, J Vet Intern Med 20:1161, 2006.

Scott JA et al: Canine pyothorax: pleural anatomy and pathophysiology, *Compend Contin Educ Pract Vet* 25:172, 2003.

# CHAPTER

### Diagnostic Tests for the Pleural Cavity and Mediastinum



#### CHAPTER OUTLINE

RADIOGRAPHY
Pleural Cavity
Mediastinum

ULTRASONOGRAPHY
COMPUTED TOMOGRAPHY
THORACOCENTESIS
CHEST TUBES: INDICATIONS AND PLACEMENT
THORACOSCOPY AND THORACOTOMY

#### RADIOGRAPHY

#### PLEURAL CAVITY

The pleura surrounds each lung lobe and lines the thoracic cavity. It is not normally visible radiographically, and individual lung lobes cannot be distinguished. Abnormalities of the pleura and pleural cavity include pleural thickening, pleural effusion, and pneumothorax. The mediastinum in the dog and cat is not an effective barrier between the left and right side of the thorax, and effusion or pneumothorax is therefore usually bilateral.

#### **Pleural Thickening**

Pleural thickening results in a thin, fluid-dense line between lung lobes, where the pleura is perpendicular to the X-ray beam. These lines arc from the periphery toward the hilar region and are known as *pleural fissure lines*. The lines can occur as a result of prior pleural disease and subsequent fibrosis, mild active pleuritis, or low-volume pleural effusion. They can be an incidental finding in older dogs. Infiltration of the pleura with neoplastic cells generally results in effusion rather than thickening.

#### **Pleural Effusion**

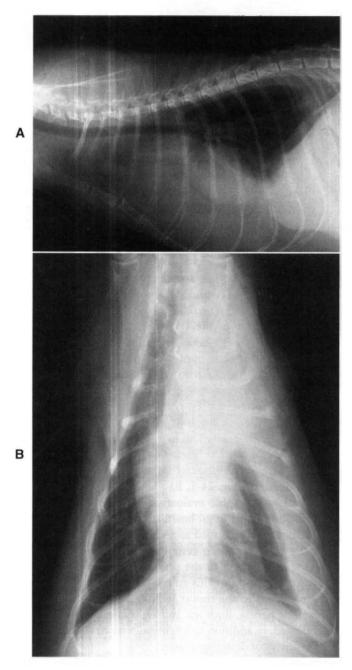
Pleural effusion is visible radiographically after about 50 to 100 ml has accumulated in the pleural cavity, depending on the size of the animal. An early effusion assumes the appear-

ance of pleural fissure lines and can be confused with pleural thickening. As fluid accumulates, the lung lobes retract and the lung lobe borders become rounded. Rounding of the caudodorsal angles of the caudal lung lobes is especially noticeable. The fluid silhouettes with the heart and diaphragm, obscuring their borders. The lungs float on top of the fluid, displacing the trachea dorsally and causing the illusion of a mediastinal mass or cardiomegaly (Fig. 24-1, A). As more fluid accumulates, the lung parenchyma appears abnormally dense as a result of incomplete expansion. Collapsed lobes should be examined carefully for evidence of torsion (see Chapter 20). Pockets of fluid accumulation or unilateral effusion indicates the possibility of concurrent pleural adhesions (Fig. 24-1, B).

Critical radiographic evaluation of intrathoracic structures, including the lungs, heart, diaphragm, and mediastinum, cannot be performed in animals with pleural effusion until the fluid has been removed. The interpretation of radiographs obtained in the presence of fluid is prone to error. An exception to this rule is the finding of gas-filled intestinal loops in the thorax, which is diagnostic for diaphragmatic hernia. Both left and right lateral views should be evaluated, in addition to a ventrodorsal view, to improve the sensitivity of detecting masses.

#### **Pneumothorax**

Pneumothorax is the presence of air in the pleural space. Air opacity without vessels or airways can be seen between the lung lobes and chest wall on radiographs. It may be necessary to carefully scrutinize the films using high intensity lighting to detect mild pneumothorax. As a greater volume of air accumulates in the pleural space, the lung parenchyma becomes more dense because of incomplete expansion, facilitating the radiographic diagnosis. The heart is generally elevated above the sternum, with air opacity apparent between these two structures (Fig. 24-2). Radiographs should be examined carefully for evidence of possible causes of the pneumothorax, such as cavitary lesions or rib fractures (indicating trauma). To accurately evaluate the pulmonary parenchyma, the air must be removed and the lungs allowed to expand. Cavitary lesions are not always apparent



**FIG 24-1 A,** Lateral thoracic view of a cat with pleural effusion. See text. **B,** Ventrodorsal view showing that the effusion is unilateral.

radiographically. Further evaluation for cavitary lesions in patients with spontaneous pneumothorax includes computed tomography.

#### **MEDIASTINUM**

The cranial and caudal mediastinum contains the heart and great vessels, esophagus, lymph nodes, and associated support structures. Radiographic abnormalities involving the mediastinum include pneumomediastinum, and alterations in size (e.g., mass lesions), displacement, and abnor-

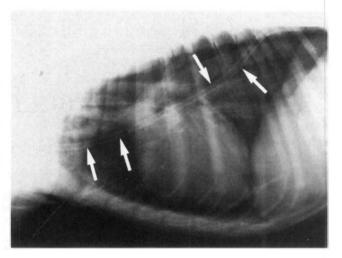


FIG 24-2

Lateral view of a dog with pneumothorax and pneumomediastinum. The pneumothorax is mild and is demonstrated by elevation of the heart above the sternum. When high-intensity lighting was placed behind the original radiographs, retraction of lung borders could also be seen. It is possible to visualize the outer wall of the trachea and major blood vessels in the anterior mediastinum because of the pneumomediastinum. A chest tube placed to stabilize the dog's condition is also visible (arrows).

malities involving the structures within the mediastinum (e.g., megaesophagus).

Pneumomediastinum is the accumulation of air in the mediastinum. If a pneumomediastinum is present, the outer wall of the trachea and the other cranial mediastinal structures, such as the esophagus, major branches of the aortic arch, and cranial vena cava, are contrasted against the air (see Fig. 24-2). These structures are not normally visible.

Abnormal soft tissue opacities can occur in the cranial mediastinum, although concurrent pleural effusion often obscures mass lesions. Localized lesions can represent neoplasia, abscesses, granulomas, or cysts (see Fig. 23-2). Less discrete disease can cause a general widening of the mediastinum that is seen to exceed the width of the vertebra on ventrodorsal views. Exudates, edema, hemorrhage, tumor infiltration, and fat can cause a widened mediastinum. Megaesophagus can often be observed in the cranial mediastinum, especially on lateral views.

The caudal vena cava and aorta are normally visible in the caudal mediastinum. The most common caudal mediastinal abnormalities are megaesophagus and diaphragmatic hernia. Megaesophagus is an important consideration in animals with respiratory signs because it is a common cause of aspiration pneumonia.

The mediastinum is normally located in the center of the thoracic cavity. An abnormal shift of the mediastinum is identified by a lateral change in the position of the heart on ventrodorsal or dorsoventral views. Atelectasis (i.e., lung lobe collapse), lobectomy, and adhesions of the mediastinum to the chest wall can all cause the mediastinum to shift

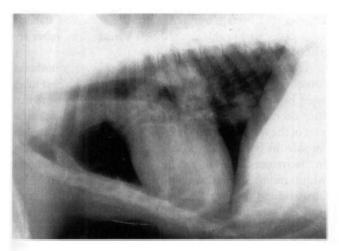


FIG 24-3

Lateral thoracic radiograph obtained in a dog with pulmonary neoplasia and sternal and hilar lymphadenopathy. The sternal node is the soft tissue opacity resting on the caudal half of the second sternebra. The hilar nodes are identified by the increased soft tissue opacity around the carina. Several discrete pulmonary nodules are also present.

toward the abnormality. Space-occupying lesions can cause the mediastinum to shift in the opposite direction.

The lymph nodes and heart are mediastinal structures but are considered separately to ensure a careful evaluation. The sternal nodes are located immediately dorsal to the sternum near the thoracic inlet at the level of the first to third sternebrae (Fig. 24-3). Enlargement is seen on lateral views and has the appearance of a discrete mass lesion. The hilar nodes are located at the heartbase around the carina. Enlargement is seen as a generalized increased soft tissue opacity in the perihilar region and is most easily seen on the lateral view. Common differential diagnoses for hilar lymphadenopathy are lymphoma and fungal infections (especially histoplasmosis). Other differential diagnoses include metastatic neoplasia, eosinophilic pulmonary granulomatosis, and mycobacterial infections. Any inflammatory disease can potentially cause lymphadenopathy. Other considerations in animals with an increased perihilar opacity on radiographs include atrial enlargement and heartbase tumors.

Evaluation of the heart is described in Chapters 1 and 2. Right-sided heart failure and pericardial effusion can cause pleural fluid accumulation.

#### **ULTRASONOGRAPHY**

Ultrasonography is indicated in the diagnostic evaluation of dogs and cats with pleural effusion to search for masses, diaphragmatic hernia, lung lobe torsion, and cardiac disease. Mediastinal masses, masses involving the pulmonary parenchyma adjacent to the body wall, and masses extending into the thorax from the body wall may be identified and their echogenicity evaluated. Ultrasonography can also be used to

guide aspiration needles or biopsy instruments to the lesion, although biopsies can be done safely only on solid masses. Ultrasonography is also useful for directing needle placement during thoracocentesis in animals with localized accumulations of pleural fluid. Air interferes with the sound waves, so structures surrounded by aerated lung cannot be examined.

#### **COMPUTED TOMOGRAPHY**

As discussed in Chapter 20, computed tomography is more sensitive than radiographs for evaluating the thorax. It is useful to determine the extent of mass lesions prior to thoracotomy and to increase the likelihood of localizing cavitary lesions in patients with spontaneous pneumothorax.

#### **THORACOCENTESIS**

Thoracocentesis is indicated for the collection of diagnostic specimens in dogs and cats with pleural effusion, for removal of pleural fluid or air to stabilize the condition of dogs and cats with impaired ventilation, and before radiographic evaluation of intrathoracic structures in dogs and cats with pleural fluid or air. Possible complications of thoracocentesis are pneumothorax caused by lung laceration, hemothorax, and iatrogenic pyothorax. Complications are extremely rare if careful technique is used.

Thoracocentesis is performed with the animal in lateral or sternal recumbency, depending on which position is less stressful. Fluid or air is usually present bilaterally throughout the pleural space and can be retrieved from the seventh intercostal space (ICS) by placing the needle approximately two thirds of the distance from the costochondral junction toward the spine. If initial attempts are unsuccessful, other sites are tried or the animal's position is changed. Fluid may be more successfully retrieved from gravity-dependent sites (i.e., closer to the costochondral junctions) and air from nondependent sites. Thoracic radiographs are useful in choosing sides for thoracocentesis in the event of unilateral effusions. Ultrasonography is useful for guiding needle placement in patients in which fluid collection proves difficult.

A local anesthetic can be administered at the site of thoracocentesis. Sedation is rarely required but may be useful for decreasing patient stress. The site is shaved and surgically prepared, and the procedure is performed using sterile technique. Most often, a butterfly catheter, three-way stopcock, and syringe are used. The removal of fluid or air by syringe is associated with movement of the syringe, and the tubing of the butterfly catheter prevents this movement from affecting the position of the needle within the thoracic cavity. Air and most fluids can be retrieved through a 21-gauge butterfly catheter. A larger needle may be required to collect extremely viscous fluids, such as fluid from feline infectious peritonitis or pyothorax. The three-way stopcock is attached

to the catheter to keep air from entering the thorax during emptying or changing of the syringe.

With the syringe snugly attached and the stopcock open between the catheter and syringe (closed to room air), the needle is advanced through the skin only. The needle and skin are then moved about two rib spaces to the actual collection site. This technique prevents air from entering the chest through the needle tract after the procedure (an unlikely scenario). The needle is then advanced into the thorax immediately in front of the rib to avoid the intercostal vessels and nerves. The needle is held with a hand resting on the chest wall so that it will not move relative to the respirations or movement of the animal. Slight negative pressure is applied to the catheter by the syringe so that entry into the pleural space is immediately identified by the recovery of fluid or air. Once the needle has entered the plcural space, the tip is aimed away from the lung by lowering the wings of the catheter toward the body wall. Ideally, the bevel of the needle should face toward the lungs.

An alternative to a butterfly catheter is an intravenous over-the-needle catheter. In large dogs a 31/4- or 51/4-inch (8- or 13-cm) 14- to 16-gauge catheter can be used. These catheters are soft and produce less trauma than butterfly catheters while in the pleural space and permit the animal to be repositioned or rolled to improve fluid or air removal. The longer length, compared with a butterfly needle, may be needed to reach the pleural space in large-breed or obese dogs. A few side holes can be added to the distal end of the catheter using a surgical blade and sterile technique to increase the sites where fluid can enter. The holes should be spaced far apart, should not take up more than one fifth of the circumference of the catheter, and should have no rough edges because the catheter might then break off in the animal during removal. Extension tubing and a three-way stopcock are attached to the catheter immediately after placement. A small skin incision, just slightly larger than the catheter, will facilitate placement. As with the butterfly catheter, slight negative pressure is maintained by syringe so that entry into the pleural space is immediately identified. The catheter tip is then directed cranially to allow positioning of the catheter between the lungs and chest wall, preventing trauma to the lung tissue.

After fluid specimens are saved for cytologic and microbiologic analysis, as much fluid or air as possible is removed, except in patients with acute hemothorax (see Chapter 26).

### CHEST TUBES: INDICATIONS AND PLACEMENT

Chest tube placement is indicated for the treatment of dogs and cats with pyothorax (see Chapter 25). Chest tubes are also indicated for the management of pneumothorax if air continues to accumulate despite multiple thoracocenteses. Chest tubes provide a means to prevent fluid and air from accumulating in the pleural space until the underlying cause of the pleural disorder resolves. If possible, needle thoraco-

centesis and therapy for shock are performed to stabilize dogs and cats in critical condition before chest tubes are placed.

The major complication of chest tubes is pneumothorax caused by a leak in the apparatus. Animals with chest tubes must be carefully monitored at all times to make sure that they do not disrupt the tubing connections, pull the tube part of the way out of the chest so that there are fenestrations outside the body wall, or bite through the tubing. Any leaks in the system can result in a life-threatening pneumothorax within minutes. If an animal with a chest tube must be left unattended, the tube should be clamped off close to the body wall and should be well protected by bandage material. Hemothorax, iatrogenic pyothorax, and pneumothorax caused by lung laceration can also occur, but these problems are generally prevented through the use of careful aseptic technique.

Pediatric chest tubes can be obtained from hospital supply companies. These tubes have multiple fenestrations, are calibrated along their length, and are radiopaque. For treating pyothorax, the tube should be as large as will fit between the ribs. The size of the tube is less critical for control of pneumothorax. Before placement the end of the tube is occluded with a syringe adapter, a three-way valve, and a hose clamp (Fig. 24-4, A).

Sterile technique is used during placement of the chest tube. In an animal with unilateral disease, the tube is placed in the involved side of the thorax. Either side can be used in an animal with bilateral disease. The lateral side of the animal over the caudal rib cage is shaved and surgically prepared. The animal is anesthetized or heavily sedated. If the animal is sedated, a local anesthetic is placed subcutaneously at the tenth ICS and within the subcutaneous tissues, intercostal muscles, and pleura at the seventh ICS. The dorsoventral orientation is one half to two thirds the distance from the costochondral junction to the thoracolumbar musculature. This distance should correspond to the level where the ribs are maximally bowed.

The length of tube to be advanced into the chest must be determined from thoracic radiographs or by external landmarks on the animal. The tube should extend from the tenth ICS to the first rib. The fenestrations in the tube must not extend outside the point of exit from the pleural cavity.

A stab incision is made through the skin at the tenth ICS. A purse-string suture is then placed around the opening but is not tied. Some chest tubes made for humans contain a stylet. Smaller chest tubes are inserted with the aid of curved hemostats. The tip of the tube is grasped with the tip of the hemostats with the tube parallel to the body of the clamps (see Fig. 24-4, *B*).

The tube, with the stylet or hemostats, is then tunneled subcutaneously from the tenth to the seventh ICS. If hemostats are used, the tips are directed away from the animal's body (see Fig. 24-4, C). Once the tip reaches the seventh ICS, the stylet or hemostats are raised perpendicular to the chest wall. The palm of the hand is placed over the end of the stylet or the hemostat handles, and the tube is thrust

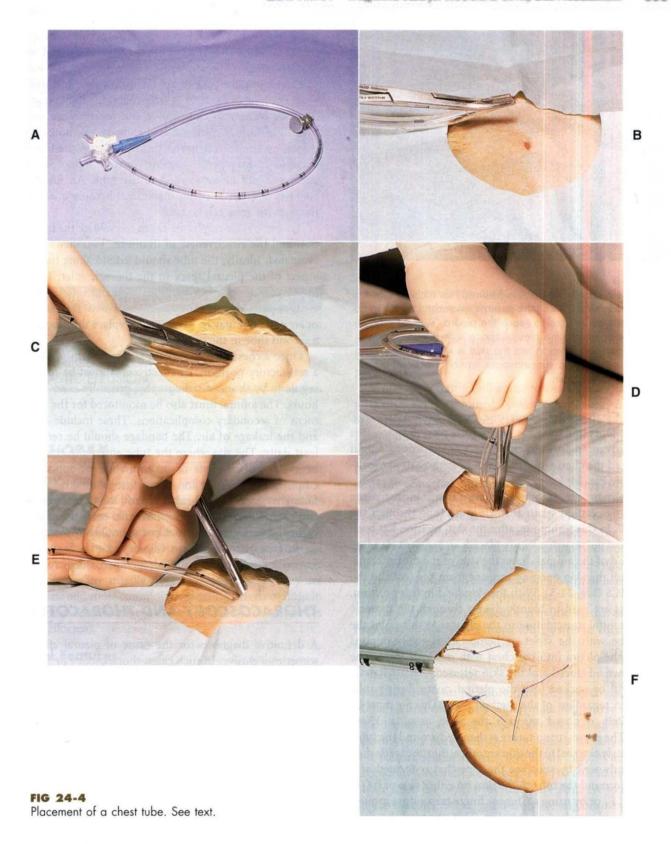




FIG 24-5

After an assistant pulls the skin forward, an incision can be made through the skin at the seventh intercostal space and blunt dissection is used to reach the pleura. A chest tube can be popped into the pleural space with minimal trauma to the underlying lung. When the skin is released, the tube will course through a subcutaneous tunnel to prevent air leaks around the tube.

through the body wall with one rapid motion (see Fig. 24-4, *D*). Once the tube has entered the pleural space, it is quickly advanced forward until the predetermined length has entered the chest while the stylet or hemostats are withdrawn (see Fig. 24-4, *E*).

An alternative technique can be used to minimize trauma to the lungs caused when thrusting the tube through the body wall. In this technique, after the skin incision has been made and a purse-string suture placed, an assistant standing at the head of the animal draws the skin of the thorax cranially to pull the skin opening forward from the tenth to the seventh ICS (Fig. 24-5). With the skin held in this position, hemostats are used to bluntly dissect through the thoracic and intercostal musculature to the pleura. At this point the chest tube with the stylet or hemostats is easily popped through the pleura into the chest with minimal force. The tube is then advanced and the skin released.

Air will be sucked into the pleural cavity during tube placement regardless of the method used. This air must be immediately removed through the tube using a 35-ml syringe. The purse-string suture is then tied around the tube. Immediately external to the skin entrance, the tube is attached to the body wall by suturing the tape that is formed as a butterfly around the tube to the skin on either side of it (see Fig. 24-4, F) or by using a Chinese finger trap suture around the tube and attached to the skin. This prevents the chest

tube from being withdrawn if tension is accidentally applied to the tubing. The opening in the skin is covered with a sterile sponge with antiseptic ointment. A light wrap is placed around the tube to hold it against the chest wall. The wrap must not be too tight. A wrap that is too tight can greatly decrease chest wall compliance and increase the work of breathing in these compromised animals. The hose clamp is placed on the tube between the animal and the three-way valve to further protect against pneumothorax whenever suction is not being applied to the tube. An Elizabethan collar is always placed on the animal because a single bite through the tube can be fatal.

Thoracic radiographs are taken to evaluate the tube position and the effectiveness of drainage. Two views must be evaluated. Ideally, the tube should extend along the ventral aspect of the pleural space to the thoracic inlet. The most important sign of adequate tube placement is the absence of areas of persistent fluid or air accumulation. If areas of fluid or air persist, it may be necessary to replace the tube or place a second tube in the opposite side.

Once a chest tube is in place and is determined to be in a satisfactory position, its effectiveness must be monitored regularly by thoracic radiography, generally every 24 to 48 hours. The animal must also be monitored for the development of secondary complications. These include infection and the leakage of air. The bandage should be removed at least daily. The site where the tube enters the skin should be evaluated for signs of inflammation or subcutaneous emphysema. The tube and skin sutures should be examined for signs of motion. The skin around the tube is kept clean, and a sterile sponge is replaced over the entry site of the tube before rebandaging. Stopcock ports should be protected with sterile caps when not in use. Gloves should be worn and the stopcock ports wiped with hydrogen peroxide before use.

#### THORACOSCOPY AND THORACOTOMY

A definitive diagnosis for the cause of pleural effusion is sometimes elusive. In such cases, thoracoscopy or thoracotomy may be necessary to allow visual assessment of the thoracic cavity and the collection of specimens for histologic and bacteriologic analysis. Mesotheliomas and pleural carcinomatosis are often diagnosed through these methods.

#### Suggested Readings

DeRycke LM et al: Thoracoscopic anatomy of dogs positioned in lateral recumbency, *J Am Anim Hosp Assoc* 37:543, 2001. Suter PF: *Thoracic radiography*, Wettswil, Switzerland, 1994, Peter F Suter.

#### CHAPTER

# Disorders of the Pleural Cavity



#### CHAPTER OUTLINE

PYOTHORAX
CHYLOTHORAX
SPONTANEOUS PNEUMOTHORAX
NEOPLASTIC EFFUSION

#### **PYOTHORAX**

#### **Etiology**

Septic exudate in the pleural cavity is referred to as *pyothorax*. It is most often idiopathic in origin, particularly in cats. It can result from foreign bodies, puncture wounds through the chest wall, esophageal tears (usually from ingested foreign bodies), and extension of pulmonary infection. Thoracic foreign bodies are usually migrating grass awns. They are rare in cats and most common in sporting breeds of dogs in states where there is a large concentration of foxtail grasses (e.g., California).

#### **Clinical Features**

Dogs and cats with pyothorax have clinical signs referable to pleural effusion and abscess formation. Signs may be acute or chronic. Tachypnea, decreased lung sounds, and increased abdominal excursions are typical of pleural effusion. In addition, fever, lethargy, anorexia, and weight loss are common. Animals may be presented in septic shock or demonstrate signs of systemic inflammatory response syndrome.

#### **Diagnosis**

The diagnosis of pyothorax is made through thoracic radiography and the cytologic evaluation of pleural fluid. Thoracic radiographs are used to confirm the presence of pleural effusion and to determine whether the disease is localized, unilateral, or bilateral. In most animals fluid is present throughout the pleural space. The finding of a localized accumulation of fluid indicates the possible presence of pleural fibrosis, mass lesions, or lung lobe torsion. Thoracic

radiographs are taken again after removal of the fluid to evaluate the pulmonary parenchyma for evidence of underlying disease (e.g., bacterial pneumonia, foreign body) that may have caused the pyothorax. The identification of a septic exudate by pleural fluid analysis establishes the diagnosis of pyothorax.

Septic suppurative inflammation is a consistent finding in pleural fluid examined cytologically, except in animals that are receiving antibiotics (Fig. 25-1; see also Chapter 23). Pleural fluid is best evaluated by Gram staining and aerobic and anaerobic bacterial cultures. Anaerobes are usually present in the fluid, and in many dogs and cats, more than one type of bacteria are present. All of the types of bacteria involved may not grow in the laboratory in spite of cytologic evidence of their presence, possibly because of competition between organisms or an inhibitory effect of the exudative fluid. Organisms such as *Actinomyces* and *Nocardia* particularly do not grow well if specimens have been cultured using routine procedures. The absence of growth of bacteria does not rule out a diagnosis of pyothorax.

Evaluation of the patient's systemic status may reveal evidence of active inflammation, systemic inflammatory response syndrome, or sepsis.

#### **Treatment**

Medical therapy for pyothorax includes antibiotics, drainage of the pleural cavity, and appropriate supportive care (e.g., fluid therapy). At first, empirically selected antibiotics are administered intravenously. The results of Gram staining and culture and sensitivity testing are helpful in selecting antibiotics. Generally, anaerobes and Pasteurella (a common isolate from cats with pyothorax) are sensitive to amoxicillin-clavulanate. Other gram-negative organisms are often sensitive to amoxicillin-clavulanate, but their antibiotic sensitivities are unpredictable. Unfortunately, this drug is not available for intravenous administration. Ampicillin with sulbactam, a different -lactamase inhibitor, is an excellent substitute for intravenous use (22 mg/kg of ampicillin q8h). Other drugs that have good activity against anaerobic organisms are chloramphenicol, metronidazole, and clindamycin. If metronidazole or clindamycin is used, additional gram-

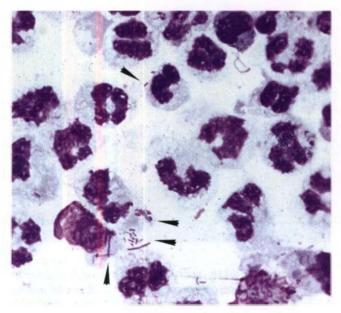


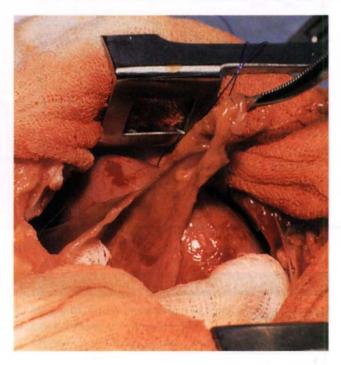
FIG 25-1
Cytologic preparation of a specimen of a pleural effusion from a cat with pyothorax. Degenerative neutrophils predominate, and intracellular and extracellular bacteria are prevalent (arrowheads). Both rods and cocci are seen.

negative coverage is necessary and is achieved by adding a fluoroquinolone or aminoglycoside antibiotic to the treatment. Addition of one of these antibiotics may also be necessary in patients receiving ampicillin with sulbactam that fail to show improvement in clinical condition, complete blood count (CBC), and fluid cytology within the first few days of treatment.

Oral antibiotics are used once significant improvement is noted, usually about the time of chest tube removal. Amoxicillin-clavulanate (20 to 25 mg/kg q8h) is used in patients that have responded to ampicillin with sulbactam. Oral antibiotic therapy is continued for an additional 4 to 6 weeks.

Drainage of the septic exudate is an essential part of the treatment of pyothorax. Although treatment with antibiotics alone often causes dramatic improvement in the animal's clinical condition initially, the signs generally recur, and complications of the prolonged infection, such as fibrosis or abscesses, are more likely (Fig. 25-2). Indwelling chest tubes provide the best drainage and can be used to keep the exudate from accumulating during the initial days of antibiotic therapy. Dogs and cats in critical condition at presentation are stabilized through the use of needle thoracocentesis and shock therapy before chest tube placement. Intermittent needle thoracocentesis is minimally effective for draining the pleural cavity and is not recommended for treatment unless the owner cannot afford the expense of chest tube management.

Chest tube placement and assessment of positioning are discussed in Chapter 24. Animals probably respond most rapidly to constant suctioning of the exudate from the chest, although intermittent suction is certainly adequate and often



Pleural fibrosis manifested by markedly thickened pleura seen during thoracotomy in a cat with chronic pyothorax. Treatment with antibiotics alone was attempted, and several weeks later the cat's condition deteriorated. Fibrosis was too extensive to allow for routine drainage with chest tubes. Surgical debridement, several lobectomies, drainage through surgically placed tubes, and long-term antibiotic therapy resulted in a cure.

more feasible. Constant suction is applied with a suction pump and collection unit. Disposable pediatric cage-side collection units (e.g., Thora-Seal III, Argyle, Sherwood Medical) are available through hospital supply companies. These units allow monitoring of collected fluid volume and adjustment of suction pressure. An initial suction pressure of 10 to 15 cm  $\rm H_2O$  is used, but more or less pressure may be necessary depending on the viscosity of the pleural fluid and the collapsibility of the tubes. The collection systems must be carefully monitored for the occurrence of leaks or malfunctions that could cause a fatal pneumothorax.

Intermittent suction by syringe is ideally performed every 2 hours for the first days of treatment, with arrangements made for drainage to continue during the night. Within a few days the volume of fluid produced will decrease, and the interval can then be lengthened. If such intensive care is not possible, an effort should still be made to empty the chest of fluid at least once late in the evening to minimize the accumulation of exudate overnight.

Lavage of the chest cavity is performed twice daily and consists of the removal of any fluid within the chest, followed by the slow infusion of warmed sterile saline solution into the chest. A volume of approximately 10 ml/kg of body weight is infused, but the infusion should be discontinued if any distress is noted. After this the animal is gently rolled

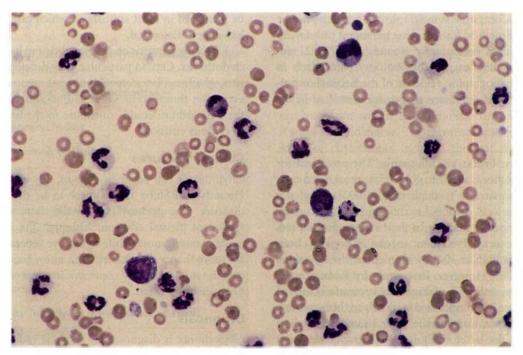


FIG 25-3
Cytologic preparation of a specimen of a pleural effusion from a cat being treated successfully for pyothorax with chest tube drainage and antibiotics. Compared with the fluid shown in Fig. 25-1, the nucleated cell count is low, the neutrophils are nondegenerative, organisms are not present, and mononuclear cells are appearing (Cytocentrifuge prep).

from side to side, and the fluid is removed. Sterile technique is used throughout the procedure. The volume recovered should be about 75% of the volume infused. If less fluid is retrieved, this may indicate that the chest tube is no longer providing adequate drainage and should be assessed by radiograph or ultrasonography. There is no obvious benefit from the addition of antibiotics, antiseptics, or enzymes to the lavage solution. The addition of heparin (1500 U/100 ml) to the lavage fluid may decrease fibrin formation.

All adapter ports connected to the chest tube should be covered with sterile caps when not in use. When accessing the ports, the clinician should wear gloves and remember to wipe the ports with hydrogen peroxide before use.

Thoracic radiographs are taken every 24 to 48 hours to ensure that the chest is being completely drained of fluid. Failure to monitor the effectiveness of drainage radiographically can lead to costly prolongation of the intensive care required for maintenance of the chest tube.

Serum electrolyte concentrations are also monitored. Many dogs and cats with pyothorax are dehydrated and anorectic at presentation and require intravenous fluid therapy. Supplementation of the intravenous fluid with potassium may be necessary.

The decision to discontinue drainage and remove the chest tube is based on the fluid volume and cytologic characteristics. The volume of fluid recovered should have decreased to less than 2 ml/kg/day. Slides of the fluid are prepared daily and evaluated cytologically. Bacteria should no longer be visible intracellularly or extracellularly. Neutro-

phils will persist but should no longer appear degenerative (Fig. 25-3). When these criteria have been met and no pockets of fluid are seen on thoracic radiographs, the chest tube is removed and the animal is monitored clinically for at least 24 hours for the development of pneumothorax or the recurrence of effusion. Thoracic radiographs can be taken to more sensitively evaluate the animal for these potential problems.

Thoracic radiographs are evaluated 1 week after removal of the chest tube and 1 week and 1 month after discontinuation of the antibiotic therapy. These radiographs are obtained so that a localized nidus of disease such as a foreign body or an abscess can be identified and also so that recurrence of a pyothorax can be detected before large volumes of pleural fluid accumulate. Such niduses are often invisible when large volumes of pleural fluid are present or while aggressive therapy is in progress.

Exploratory thoracotomy is indicated for the removal of a suspected nidus of infection and in those animals that do not respond to medical therapy. In the latter instance surgery may be necessary to remove fibrotic and diseased tissue or a foreign body. Failure to respond is suggested by the continued need for a chest tube for longer than 1 week after the start of appropriate antibiotic treatment and drainage, although reported cases that have undergone complete recovery after medical management have required drainage by chest tubes for longer periods. Furthermore, persistence of large pockets of fluid in spite of appropriate chest tube placement may necessitate the decision to perform a thora-

cotomy earlier. Computed tomography of the chest may be a more sensitive method for detecting persistent pulmonary lesions than thoracic radiography. Rooney et al. (2002) recommended consideration for thoracotomy particularly in dogs that have radiographic evidence of mediastinal or pulmonary lesions or if *Actinomyces* spp. are identified in the pleural fluid.

#### **Prognosis**

Most cases of pyothorax are idiopathic. The prognosis for animals with pyothorax is fair to good if it is recognized early and treated aggressively. Waddell et al. (2002) reported a survival rate for cats of 66%, excluding those that were euthanatized before treatment. In their report, 5 of 80 cats required thoracotomy. Treatment success in dogs has been reported to be as high as 100% with medical therapy alone (Piek et al., 2000). However, in a study by Rooney et al. (2002) of 26 dogs, only 25% of dogs were successfully treated medically whereas 78% responded favorably to thoracotomy. One possible explanation for the poor success of medical management in the latter study is the geographic location in a region of the country where grass awn migration is common.

Exploratory surgery is necessary to ensure complete resolution of the problem in dogs or cats with foreign bodies in the thoracic cavity. Radiolucent foreign bodies can be difficult to find, however, and the prognosis for pyothorax secondary to them is more guarded. Long-term complications of pyothorax such as pleural fibrosis and restrictive lung disease are uncommon.

#### **CHYLOTHORAX**

#### Etiology

Chylothorax is the accumulation of chyle within the thoracic cavity. The chyle originates from the thoracic duct, which carries triglyceride-rich fluid from the intestinal lymphatics and empties into the venous system in the anterior thorax. The fluid also contains lymphocytes, protein, and fat-soluble vitamins. Thoracic duct rupture after thoracic trauma can result in transient chylothorax. However, most cases are not the result of a ruptured duct. Possible causes of nontraumatic chylothorax include generalized lymphangiectasia, inflammation, and obstruction of lymphatic flow. Flow can be obstructed for physical reasons, such as neoplasia, or as a result of increased venous pressures.

Chylothorax can be categorized as congenital, traumatic, or nontraumatic. A congenital predisposition may exist in animals in which chylothorax develops later in life. Traumatic events that induce chylothorax can be surgical (e.g., thoracotomy) or nonsurgical (e.g., being hit by a car). Nontraumatic causes of chylothorax include neoplasia, particularly mediastinal lymphoma in cats; cardiomyopathy, dirofilariasis, pericardial disease, and other causes of right-sided heart failure; lung lobe torsion; diaphragmatic hernia; and systemic lymphangiectasia. No underlying disease can

be identified in most animals, in which case idiopathic chylothorax is diagnosed.

Fibrosing pleuritis and pericarditis can be associated with chylothorax. Cats, in particular, may develop fibrosing pleuritis, which can interfere with normal expansion of the lungs even after thoracocentesis. Inflammation and thickening of the pericardium could contribute to the further formation of chylous effusion.

#### **Clinical Features**

Chylothorax can occur in dogs or cats of any age. Afghan Hounds and Shiba Inus appear to be predisposed to the disorder. The primary clinical sign is respiratory distress typical of pleural effusion. Although the distress is often acute in onset, more subtle signs have generally been present for more than a month. Lethargy, anorexia, weight loss, and exercise intolerance are common. In some cases cough is the only presenting sign.

#### Diagnosis

Chylothorax is diagnosed by thoracic radiographs and the identification of chyle through cytologic and biochemical evaluation of pleural fluid obtained by thoracocentesis (see Chapter 23). Lymphopenia and panhypoproteinemia may be present in peripheral blood.

Once chylothorax has been diagnosed, further diagnostic tests are performed to identify potential underlying disease (Box 25-1). These tests include thoracic ultrasonography; echocardiography; microfilarial examination and adult antigen testing for heartworm disease; and, in cats, the measurement of thyroid hormone concentrations. Lymphangiography can be used to identify lymphangiectasia, sites of obstruction, and, rarely, sites of leakage from the thoracic duct. Lymphangiography is performed before the surgical ligation of lymphatics is attempted.

#### **Treatment**

Thoracocentesis and appropriate fluid therapy are used to stabilize dogs and cats with chylothorax, as needed, at presentation. Electrolyte abnormalities may be present. A concerted effort is made to identify any underlying cause of the chylothorax so that it can be directly treated. Elimination of the underlying problem may result in resolution of the chylothorax, although medical management (as described later for idiopathic chylothorax) is generally required for several weeks or even months. The exception is chylothorax of traumatic origin, which generally resolves within 1 to 2 weeks.

A routinely successful treatment for idiopathic chylothorax has not been established. Medical management is initially attempted because spontaneous remission occurs in some cases. In the absence of resolution with medical therapy, thoracic duct ligation and pericardectomy are recommended.

Medical management consists primarily of intermittent thoracocentesis and a low-fat diet. Thoracocentesis is performed as needed on the basis of the owner's observation of increased respiratory rate or effort or decreased activity or



回 BOX 25-1

Diagnostic Tests to Identify Underlying Diseases in Dogs and Cats with Chylothorax

#### Complete Blood Count, Serum Biochemical Panel, Urinalysis

Evaluation of systemic status

#### Cytologic Examination of Fluid

Infectious agents

Neoplastic cells (especially lymphoma)

#### Thoracic Radiographs (After Fluid Removal)

Anterior mediastinal masses

Other neoplasia

Cardiac disease

Heartworm disease

Pericardial disease

#### Ultrasonography (Ideally, in the Presence of Fluid)

Anterior mediastinum

Mass

Heart (echocardiography)

Cardiomyopathy

Heartworm disease

Pericardial disease

Congenital heart disease

Other fluid densities adjacent to body wall

Neoplasia

Lung lobe torsion

#### **Heartworm Antibody and Antigen Tests**

Heartworm disease

#### Lymphangiography

Preoperative and postoperative assessment of thoracic duct

appetite. Initially, thoracocentesis may need to be performed every 1 to 2 weeks. The interval between thoracocenteses will gradually lengthen if the chylothorax is responsive to medical management. Ultrasound guidance of the needle during thoracocentesis is especially helpful in removing pockets of chyle from the pleural cavity, and by increasing the effectiveness of drainage, it can prolong the interval between thoracocenteses.

A low-fat, nutritionally complete diet is fed (see Chapter 54). In humans medium-chain triglyceride oil is absorbed directly into the bloodstream, bypassing the lymphatics, and can be used as a fat supplement. Unfortunately, in dogs these triglycerides have been shown to enter the thoracic duct. Nevertheless, they can be added to the diet if additional calories are desired.

Medical management may be facilitated by the administration of rutin, a benzopyrone drug. Rutin has been used in humans for the treatment of lymphedema. It is thought to decrease the protein content of the effusion by affecting macrophage function. The resorption of effusion may thereby be enhanced and fibrosis of the pleura minimized. The drug is available over the counter at health food stores. A dosage of 50 to 100 mg/kg given orally every 8 hours is recommended.

Surgical management is considered if clinical signs have not improved within 2 to 3 months of medical therapy or if signs are intolerable. The recommended surgical management of chylothorax includes thoracic duct ligation and pericardectomy. Thoracic duct ligation is technically difficult and is ideally performed by an experienced surgeon. Multiple ligations of the thoracic duct and its collaterals are performed. The ducts are identified by lymphangiography before surgery, and lymphangiography is repeated after ligation to assess the success of ligation. Pericardectomy is recommended at the time of thoracic duct ligation and is associated with an improved outcome (Fossum et al., 2004).

Placement of pleuroperitoneal or pleurovenous shunts or mesh within the diaphragm to allow fluid to drain away from the pleural space has also been recommended for the management of chylothorax and should be considered if medical and surgical treatment are unsuccessful. These drainage procedures provide a route for the leaking chyle to reenter the circulation without producing the respiratory compromise associated with pleural effusion. Unfortunately, drains often become nonfunctional within months of placement.

#### **Prognosis**

The prognosis for chylothorax has generally been regarded as guarded unless the chylothorax was traumatically induced or the result of a reversible condition. However, a study by Fossum et al. (2004) indicated an overall success rate for thoracic duct ligation and pericardectomy of 100% in dogs and 90% in cats. It is not possible to predict the contribution of fibrosing pleuritis to clinical signs in cats with this complication. In cats with continued respiratory difficulties following resolution of effusion, decortication of the lung is considered.

#### SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax occurs when preexisting pulmonary cavitary lesions rupture. It is much less common than traumatic pneumothorax and occurs more often in dogs than cats. Rapid, profound respiratory distress occurs in the subset of animals in which a tension pneumothorax develops. Cavitary lesions can be congenital or idiopathic or result from prior trauma, chronic airway disease (e.g., idiopathic feline bronchitis), or Paragonimus infection. Necrotic centers can develop in neoplasms, thromboembolized regions (e.g., from dirofilariasis), abscesses, and granulomas involving the airways, and these can rupture, allowing air to escape into the pleural space. (See Chapter 20 for further discussion of cavitary lesions.)

Thoracocentesis is useful for initial stabilization of the animal's condition. If frequent thoracocentesis is needed to



Blebs can be seen in this intra-operative image of the lung of a dog that presented with spontaneous pneumothorax. The size of these blebs precluded their identification by either thoracic radiography or computed tomography. (Courtesy Dr. Guillaume Pierre Chanoit.)

control the pneumothorax, a chest tube is placed (see Chapter 24). Dogs and cats are evaluated for underlying disease with thoracic radiographs (repeated after full lung expansion), computed tomography of the thorax, multiple fecal examinations for *Paragonimus* ova (see Chapter 20), heartworm tests, and possibly tracheal wash fluid analysis or bronchoscopy. Computed tomography is much more sensitive for the identification of bullae or blebs and should be performed before thoracotomy. In a study by Au et al. (2006), thoracic radiography identified bullae or blebs in only 2 of 12 dogs with spontaneous pneumothorax whereas computed tomography was successful in identifying lesions in 9 of these dogs.

Patients with Paragonimus infections generally respond to medical treatment (See Chapter 22). Otherwise, surgical therapy is indicated for most animals. In a review of 21 cases, Holtsinger et al. (1993) found that most dogs with spontaneous pneumothorax managed medically with chest tubes and suction ultimately required surgery during the initial hospitalization or upon subsequent recurrence of pneumothorax to resolve the problem. Because unobserved recurrence of spontaneous pneumothorax can be fatal, conservative treatment is believed to carry more risk than surgery. Furthermore, a report of 64 cases by Puerto et al. (2002) showed that recurrence and mortality rates for dogs with spontaneous pneumothorax were lower in dogs that had surgery compared with dogs that were treated conservatively. A median sternotomy is generally recommended to allow exposure of all lung lobes because it is often not possible to localize all cavitary lesions preoperatively (Fig. 25-4). Abnormal tissue is evaluated histologically and microbiologically for a definitive diagnosis.

Conservative therapy consists of cage rest and chest tube placement with continuous suction (see the section on pyothorax). In large dogs a one-way Heimlich valve can be used rather than suction.

Regardless of the treatment used, recurrence is a possibility. Accurate diagnosis of the underlying lung disease and determination of the extent of involvement through a thoracotomy assist in determining the prognosis.

#### **NEOPLASTIC EFFUSION**

Neoplastic effusions resulting from mediastinal lymphoma are treated with radiation or chemotherapy (see Chapter 80). Effusions caused by mesothelioma or carcinoma of the pleural surfaces may respond to palliative therapy with intracavitary infusions of cisplatin or carboplatin (see Moore, 1992). Placement of pleuroperitoneal shunts or intermittent thoracocentesis to alleviate the degree of respiratory compromise can also be considered to prolong the life of patients that have no clinical signs beyond those resulting from the accumulation of pleural effusion.

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# CHAPTER Emergency Management of Respiratory Distress

#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS LARGE AIRWAY DISEASE

Extrathoracic (Upper) Airway Obstruction Intrathoracic Large Airway Obstruction PULMONARY PARENCHYMAL DISEASE PLEURAL SPACE DISEASE

#### GENERAL CONSIDERATIONS

Respiratory distress, or dyspnea, refers to an abnormally increased effort in breathing. Some authors prefer to use terms such as hyperpnea and increased respiratory effort in reference to this abnormality because dyspnea and distress imply feelings that cannot be determined with certainty in animals. Breathing difficulties are extremely stressful for people and are likely so for dogs and cats as well. Dyspnea is also physically exhausting to the animal as a whole and to the respiratory musculature specifically. Animals in respiratory distress at rest should be managed aggressively, and their clinical status should be frequently assessed.

A dog or cat in respiratory distress may show orthopnea, which is a difficulty in breathing in certain positions. Animals with orthopnea will assume a sitting or standing position with their elbows abducted and neck extended. Movement of the abdominal muscles that assist ventilation may be exaggerated. Cats normally have a minimal visible respiratory effort. Cats that show noticeable chest excursions or openmouth breathing are severely compromised. Cyanosis, in which normally pink mucous membranes are bluish, is a sign of severe hypoxemia and indicates that the increased respiratory effort is not sufficiently compensating for the degree of respiratory dysfunction. Pallor of the mucous membranes is a more common sign of acute hypoxemia resulting from respiratory disease than is cyanosis.

Respiratory distress caused by respiratory tract disease most commonly develops as a result of large airway obstruc-

tion, severe pulmonary parenchymal or vascular disease (i.e., pulmonary thromboembolism), pleural effusion, or pneumothorax. Respiratory distress can also occur as a result of primary cardiac disease causing decreased perfusion, pulmonary edema, or pleural effusion (see Chapter 1). In addition, noncardiopulmonary causes of hyperpnea must be considered in animals with apparent distress, including severe anemia, hypovolemia, acidosis, hyperthermia, and neurologic disease. Normal breath sounds may be increased in dogs and cats with these diseases, but crackles or wheezes are not expected.

A physical examination should be performed rapidly, paying particular attention to the breathing pattern, auscultatory abnormalities of the thorax and trachea, pulses, and mucous membrane color and perfusion. Attempts at stabilizing the animal's condition should then be made before initiating further diagnostic testing.

Dogs and cats in shock should be treated appropriately (see Chapter 30). Most animals in severe respiratory distress benefit from decreased stress and activity, placement in a cool environment, and oxygen supplementation. Cage rest is extremely important, and the least stressful method of oxygen supplementation should be used initially (see Chapter 27). An oxygen cage achieves both these goals, with the disadvantage that the animal is inaccessible. Sedation of the animal may be beneficial (Box 26-1). More specific therapy depends on the location and cause of the respiratory distress (Table 26-1).

#### LARGE AIRWAY DISEASE

Diseases of the large airways result in respiratory distress by obstructing the flow of air into the lungs. For the purposes of these discussions, extrathoracic large airways (otherwise known as *upper airways*) include the pharynx, larynx, and trachea proximal to the thoracic inlet; intrathoracic large airways include the trachea distal to the thoracic inlet and bronchi. Animals presenting in respiratory distress caused by large airway obstruction typically have a markedly increased respiratory effort with a minimally increased respiratory rate



BOX 26-1

Drugs Used to Decrease Stress in Animals with Respiratory Distress

#### Upper Airway Obstruction: Decreases Anxiety and Lessens Respiratory Efforts, Decreasing Negative Pressure within Upper Airways

Acepromazine

Dogs and cats

0.05 mg/kg IV, SQ

Morphine

Dogs only, particularly

0.1 mg/kg IV; repeat q3min to effect; duration, 1-4 hr

brachycephalic dogs

#### Pulmonary Edema: Decreases Anxiety; Morphine Reduces Pulmonary Venous Pressure

Morphine

Dogs only

0.1 mg/kg IV; repeat q3min to effect; duration, 1-4 hr

Acepromazine

Dogs and cats

0.05 mg/kg IV, SQ; duration, 3-6 hr

#### Rib Fractures, After Thoracotomy, Other Trauma: Pain Relief

Hydromorphone

Dogs

0.05 mg/kg IV, IM; can repeat IV a3mim to effect; duration, 2-4 hr

Cats

0.025-0.05 mg/kg IV, IM; can repeat IV q3min to effect but stop if mydriasis

occurs; duration, 2-4 hr

Butorphanol Buprenorphine Cats

0.1 mg/kg IV, IM, SQ; can repeat IV q3min to effect; duration, 1-6 hr

Dogs and cats 0.005 mg/kg IV, IM; repeat to effect; duration, 4-8 hr

IV, Intravenously; SQ, subcutaneously; IM, intramuscularly.



TABLE 26-1

Localization of Respiratory Tract Disease by Physical Examination Findings in Dogs and Cats with Severe Respiratory Distress

	LARGE AIRWAY DISEASE		PULMONARY PARENCHYMAL DISEASE		PLEURAL SPACE DISEASE	
	EXTRATHORACIC (UPPER)	INTRATHORACIC	OBSTRUCTIVE	RESTRICTIVE	OBSTRUCTIVE AND RESTRICTIVE	
Respiratory rate	N1-↑	N1-T	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	<b>↑</b> ↑↑	$\uparrow\uparrow\uparrow$
Relative effort	↑↑↑ Inspiration	↑↑ Expiration	↑ Expiration	↑↑ Inspiration	No difference	1 Inspiration
Audible sounds	Inpiratory stridor, stertor	Expiratory cough/wheeze	Rarely expiratory wheeze	None	None	None
Auscultable sounds	Referred upper airway sounds;  11 breath sounds	End expiratory click; 11 breath sounds	Expiratory wheezes or ↑↑ breath sounds; rarely, ↓ breath sounds with air trapping	↑↑ Breath sounds; ± crackles	↑↑ Breath sounds, crackles, and/or wheezes	↓ Breath sounds

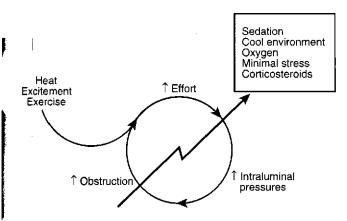
<sup>1,</sup> Slightly increased; 11, increased; 111, markedly increased; 1, decreased; N1, normal. Normal respiratory rates for dogs and cats at rest are  $\leq 20$ /min. In the hospital setting, rates of  $\leq 30$ /min are generally accepted as normal.

(see Table 26-1). Excursions of the chest may be increased (i.e., deep breaths are taken). Breath sounds are often increased.

#### EXTRATHORACIC (UPPER) AIRWAY OBSTRUCTION

Patients with extrathoracic (upper) airway obstruction typically have the greatest breathing effort during inspiration, which is generally prolonged relative to expiration. Stridor or stertor is usually heard, generally during inspiration. A history of voice change may be present with laryngeal disease.

Laryngeal paralysis and brachycephalic airway syndrome are the most common causes of upper airway obstruction (see Chapter 18). Other laryngeal and pharyngeal diseases are listed in Boxes 16-1 and 16-2. Severe tracheal collapse can result in extrathoracic or intrathoracic large airway obstruction or both. Rarely, other diseases of the extrathoracic



Patients with extrathoracic (upper) airway obstruction often present in acute respiratory distress because of a progressive worsening of airway obstruction after an exacerbating event. Medical intervention is nearly always successful in

breaking this cycle and stabilizing the patient's respiratory

status.

trachea, such as foreign body, stricture, neoplasia, granuloma, and hypoplasia, result in respiratory distress.

Patients with extrathoracic airway obstruction usually present with acute distress in spite of the chronic nature of most of these diseases because of a vicious cycle of increased respirations leading to increased obstruction, as described in Chapter 16. This cycle can almost always be broken with medical management (Fig. 26-1). The patient is sedated (see Box 26-1) and provided a cool, oxygen-rich environment (e.g., oxygen cage). For dogs with pharyngeal disease, primarily brachycephalic airway syndrome, morphine is given. Otherwise, acepromazine is used. Subjectively, dogs with brachycephalic airway syndrome seem to have more difficulty maintaining a patent airway when sedated with acepromazine compared with morphine. Short-acting corticosteroids are thought by some to be effective in decreasing local inflammation (e.g., dexamethasone, 0.1 mg/kg intravenously [IV], or prednisolone sodium succinate, up to 10 mg/kg IV).

In rare cases, sedation and oxygen supplementation will not resolve the respiratory distress and the obstruction must be physically bypassed. Placement of an endotracheal tube is generally effective. A short-acting anesthetic agent is administered. Long and narrow endotracheal tubes with stylets should be available to pass by large or deep obstructions. If an endotracheal tube cannot be placed, a transtracheal catheter can be inserted distal to the obstruction (see Chapter 27). If a tracheostomy tube is needed, it can then be placed under controlled, sterile conditions. It is rarely necessary to perform a nonsterile emergency tracheostomy.

#### INTRATHORACIC LARGE AIRWAY OBSTRUCTION

Respiratory distress caused by intrathoracic large airway obstruction is rare. Patients with intrathoracic large airway

obstruction typically have the greatest breathing effort during expiration, which is generally prolonged relative to inspiration. The most common cause of intrathoracic large airway obstruction is collapse of the mainstem bronchi and/or intrathoracic trachea (tracheobronchomalacia; see Chapter 21). A high-pitched, wheezing, coughlike sound is often heard during expiration in these patients, and crackles or wheezes may be auscultated. Other differential diagnoses include foreign body, advanced *Oslerus* infection, tracheal neoplasia, tracheal stricture, and bronchial compression by extreme hilar lymphadenopathy.

Sedation, oxygen supplementation, and minimizing stress as described for the management of upper airway obstruction are often effective in stabilizing these patients as well. High doses of hydrocodone or butorphenol will provide cough suppression and sedation (see Chapter 21). Dogs with chronic bronchitis may benefit from bronchodilators and corticosteroids.

#### PULMONARY PARENCHYMAL DISEASE

Diseases of the pulmonary parenchyma result in hypoxemia and respiratory distress through a variety of mechanisms, including the obstruction of small airways (obstructive lung disease; e.g., idiopathic feline bronchitis); decreased pulmonary compliance (restrictive lung disease, "stiff" lungs; e.g., pulmonary fibrosis); and interference with pulmonary circulation (e.g., pulmonary thromboembolism). The majority of patients with pulmonary parenchymal disease, such as those with pneumonias or pulmonary edema, develop hypoxemia through a combination of these mechanisms that contribute to V/Q mismatch (see Chapter 20), including airway obstruction and alveolar flooding, and decreased compliance.

Animals presenting in respiratory distress caused by pulmonary parenchymal disease typically have a markedly increased respiratory rate (see Table 26-1). Patients with primarily obstructive disease, usually cats with bronchial disease, may have prolonged expiration relative to inspiration with increased expiratory efforts. Expiratory wheezes are commonly auscultated. Patients with primarily restrictive disease, usually dogs with pulmonary fibrosis, may have prolonged inspiration relative to expiration and effortless expiration. Crackles are commonly auscultated. Occasionally, cats with severe bronchial disease will develop a restrictive breathing pattern in association with air trapping and hyperinflation of the lungs. Other patients, with a combination of these processes occurring, have increased efforts during both phases of respiration; shallow breathing; and crackles, wheezes, or increased breath sounds on auscultation. Differential diagnoses for dogs and cats with pulmonary disease are provided in Box 19-1.

Oxygen therapy is the treatment of choice for stabilizing dogs or cats with severe respiratory distress believed to be caused by pulmonary disease (see Chapter 27). Broncho-dilators, diuretics, or glucocorticoids can be considered

as additional treatments if oxygen therapy alone is not adequate.

Bronchodilators, such as short-acting theophyllines or  $\beta$ -agonists, are used if obstructive lung disease is suspected because they decrease bronchoconstriction. In combination with oxygen, they are the treatment of choice for cats with signs of bronchitis (see Chapter 21). Subcutaneous terbutaline (0.01 mg/kg, repeated in 5 to 10 minutes if necessary) or albuterol administered by metered dose inhaler are most often used in emergency situations. Bronchodilators are described in more detail in Chapter 21 (see pp. 290 and 296 and Box 21-2).

Diuretics, such as furosemide (2 mg/kg, administered intravenously), are indicated for the management of pulmonary edema. If edema is among the differential diagnoses of an unstable patient, a short trial of furosemide therapy is reasonable. However, potential complications of diuretic use resulting from volume contraction and dehydration should be taken into consideration. Continued use of diuretics is contraindicated in animals with exudative lung disease or bronchitis because systemic dehydration results in the drying of airways and airway secretions. The mucociliary clearance of airway secretions and contaminants is decreased, and airways are further obstructed with mucus plugs.

Glucocorticoids decrease inflammation. Rapid-acting formulations, such as prednisolone sodium succinate (up to 10 mg/kg, administered intravenously), are indicated for animals in severe respiratory distress caused by the following conditions: idiopathic feline bronchitis, thromboembolism after adulticide treatment for heartworms, allergic bronchitis, pulmonary parasitism, and respiratory failure soon after the initiation of treatment for pulmonary mycoses. Animals with other inflammatory diseases or acute respiratory distress syndrome may respond favorably to glucocorticoid administration. The potential negative effects of corticosteroids must be considered before their use. For example, the immunosuppressive effects of these drugs can result in the exacerbation of an infectious disease. Although the use of short-acting corticosteroids for the acute stabilization of such cases probably will not greatly interfere with appropriate antimicrobial therapy, long-acting agents and prolonged administration should be avoided. Glucocorticoid therapy potentially interferes with the results of future diagnostic tests, particularly if lymphoma is a differential diagnosis. Appropriate diagnostic tests are performed once the patient can tolerate the stress.

Broad-spectrum antibiotics are administered if there is evidence of sepsis (e.g., fever, neutrophilic leukocytosis with left shift and moderate to marked toxicity of neutrophils) or a high degree of suspicion of bacterial or aspiration pneumonia. Note that airway specimens (usually tracheal wash) should be obtained for culture if at all possible before initiating broad-spectrum antibiotics in order to confirm the diagnosis of bacterial infection and to obtain susceptibility data.

Specimens obtained after initiating antibiotics are often not diagnostic, even with continued progression of signs. However, airway sampling may not be possible in these unstable patients. If sepsis is suspected, blood and urine cultures may be useful. The diagnosis and treatment of bacterial and aspiration pneumonia are described in Chapter 22.

If the dog or cat does not respond to this management, it may be necessary to intubate the patient and institute positive-pressure ventilation (see Chapter 27) until a diagnosis can be established and specific therapy initiated.

#### PLEURAL SPACE DISEASE

Pleural space diseases cause respiratory distress by preventing normal lung expansion. They are similar mechanistically to restrictive lung disease. Animals presenting in respiratory distress as a result of pleural space disease typically have a markedly increased respiratory rate (see Table 26-1). Relatively increased inspiratory efforts may be noted but are not always obvious. Decreased lung sounds on auscultation distinguish patients with tachypnea caused by pleural space disease from patients with tachypnea caused by pulmonary parenchymal disease. Increased abdominal excursions during breathing may be noted.

Most patients in respiratory distress resulting from pleural space disease have pleural effusion or pneumothorax (see Chapter 23). Other differential diagnoses are diaphragmatic hernia and mediastinal masses. If pleural effusion or pneumothorax is suspected to be causing respiratory distress, needle thoracocentesis (see Chapter 24) should be performed immediately before further diagnostic testing is performed or any drugs are administered. Oxygen can be provided by mask while the procedure is performed, but successful drainage of the pleural space will quickly improve the animal's condition. Occasionally, emergency placement of a chest tube is necessary to evacuate rapidly accumulating air (see Chapter 24).

As much fluid or air should be removed as possible. The exception is in animals with acute hemothorax. Hemothorax is usually the result of trauma or rodenticide intoxication. The respiratory distress associated with hemothorax is often the result of acute blood loss rather than an inability to expand the lungs. In this situation, as little volume as is needed to stabilize the animal's condition is removed. The remainder will be reabsorbed (autotransfusion), to the benefit of the animal. Aggressive fluid therapy is indicated.

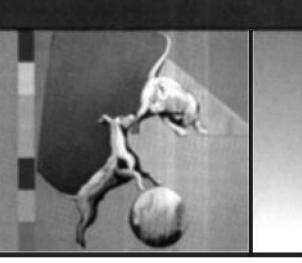
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# CHAPTER

# Ancillary Therapy: Oxygen Supplementation and Ventilation



#### CHAPTER OUTLINE

**OXYGEN SUPPLEMENTATION** 

Oxygen Masks Oxygen Hoods

Nasal Catheters

Transtracheal Catheters

**Endotracheal Tubes** 

Tracheal Tubes

Oxygen Cages

VENTILATORY SUPPORT

#### **OXYGEN SUPPLEMENTATION**

Oxygen supplementation is generally indicated to maintain arterial blood oxygen pressures (PaO<sub>2</sub>) at more than 60 mm Hg. Oxygen supplementation is indicated in every dog or cat with signs of respiratory distress or labored breathing. Cyanosis is another clear indication. Whenever possible, the cause of hypoxemia should be identified and specific treatment initiated as well. Assisted ventilation is indicated for animals with an inadequate arterial oxygen concentration despite supplementation and for animals with arterial carbon dioxide pressures exceeding 60 mm Hg (see Chapter 20).

The inhaled concentration of oxygen can be supplemented by the administration of 100% oxygen by mask, hood, nasal catheter, transtracheal catheter, endotracheal tube, tracheal tube, or oxygen cage. Administration of oxygen by nasal catheter is very well suited to most practices.

When administering 100% oxygen to an animal, the clinician must consider the anhydrous nature of pure oxygen and the toxic effects of oxygen in a high concentration. Because oxygen from tanks contains no water, drying of the airways can occur quickly, particularly if the nasal cavity has been completely bypassed by catheters or tubes. All animals with respiratory tract diseases should be systemically hydrated. Moisture must be added to the airways of animals receiving oxygen by catheter or tube for longer than a few hours. Ven-

tilators designed for long-term use have a heated humidifier incorporated into their design. Humidity exchange filters, which can also be attached to tracheal and endotracheal tubes, function by retaining moisture from exhaled air and adding it to inhaled air. These filters can support bacterial growth and must be replaced daily. Nebulization can also be used to add moisture to the airways. Less effective methods of hydration can be used if other options are not available, such as instillation of sterile 0.9% sodium chloride solution directly into tubes or catheters. Some water vapor can also be added to the oxygen by incorporating pass-over or bubble humidifiers in the system.

The inhalation of air with greater than 50% oxygen is toxic to the pulmonary epithelium. Pulmonary function deteriorates, and death can result. Air with greater than 50% oxygen is therefore not provided for longer than 12 hours. If higher concentrations are necessary to maintain adequate arterial oxygen concentrations, ventilatory support is initiated.

#### **OXYGEN MASKS**

Oxygen masks are useful for short-term supplementation. The animal experiences minimal stress, and manipulations such as venous catheter placement and thoracocentesis can be performed. A snug fit is desirable to decrease the volume of dead space, and a relatively high flow rate is necessary (Table 27-1). Sterile eye ointment is applied to prevent desiccation of the corneas.

#### **OXYGEN HOODS**

Oxygen hoods that can be placed over the animal's head are available. With some, the animals must be laterally recumbent and still, limiting the use of hoods to animals recovering from anesthesia, those that are severely depressed, and those that are heavily sedated (Fig. 27-1). Others are designed to completely surround the animal's head and are attached around the neck. One design is an adaptation of an Elizabethan collar (OxyHood, Jorgensen Laboratories, Inc.). In some situations oxygen hoods may be better tolerated than oxygen masks, and it may take less manpower to care for an animal for which one is being used than an animal with an



TABLE 27-1

Maximum Achievable Oxygen Concentrations and Associated Flow Rates for Various Methods of Supplementation

METHOD OF ADMINISTRATION	MAXIMUM OXYGEN CONCENTRATION (%)	FLOW RATE	
Mask	50-60	8-12 L/min	
Nasal catheter	50	6-8 L/min or 50-150 mL/kg/min	
Transtracheal catheter	30-40	1-2 L/min	
Endotracheal tube	100	0.2 L/kg/min	
Tracheal tube	100	0.2 L/kg/min	
Oxygen cage	60	2-3*	

From Court MH et al: Inhalation therapy: oxygen administration, humidification, and aerosol therapy, Vet Clin North Am Small Anim Pract 15:1041, 1985.

<sup>\*</sup> After cage is filled, flow is adjusted based on oxygen concentration as measured by oxygen sensor.



FIG 27-1

An oxygen hood can be used for recumbent animals as a substitute for an oxygen mask. In this patient oxygen is being delivered through an opening in the top of the hood, and the light blue opening that will accommodate standard anesthesia tubing is left open for circulation of air. Regardless of the method used to increase the oxygen in inspired air, a means for escape of expired CO<sub>2</sub> is essential. (Disposa-Hood, Utah Medical Products, Inc., Midvale, Utah.)

oxygen mask. A means for escape of exhaled air must always be provided to prevent the buildup of CO<sub>2</sub> within the hood.

#### **NASAL CATHETERS**

Nasal catheters can be used for long-term oxygen supplementation (Fig. 27-2). The animal is relatively free to move and is accessible for evaluation and treatment. Most animals tolerate the catheter well. Catheters can become obstructed



FIG 27-2

Dog with intranasal catheter in place for delivery of oxygen. The catheter is sutured to the muzzle less than 1 cm from its exit from the naris and is further anchored with sutures to the face so that it exits behind the animal's head. An Elizabethan collar is routinely used to prevent the animal from removing the catheter.

with nasal secretions, however. Soft red rubber or infant feeding tubes or polyurethane catheters can be used. Tube size is based on patient size. In general, a 3.5 to 5 French tube is used for cats, and a 5 to 8 French tube is used for dogs.

The method of placement has been described by Fitzpatrick et al. (1986). First, the length of tubing to be inserted into the nasal cavity is measured against the head of the animal. The tubing should reach the level of the carnassial tooth. Sedation is rarely necessary. A water-soluble lubricant or 0.2% lidocaine jelly is applied to the length of the catheter that will be within the nasal cavity. Next, 0.2% lidocaine is dripped gently into the nasal cavity through the naris with the animal's nose pointed upward. The catheter is then passed through the naris, initially aimed dorsomedially

through the naris, then immediately ventromedially. Once the correct length of catheter has been inserted, it is gently bent beneath the lateral cartilage and sutured to the muzzle no farther than 1 cm caudal to the exit from the naris. The catheter can be further anchored to the face with sutures, traveling between the eyes to behind the animal's head. An Elizabethan collar is placed on the patient to prevent the animal from removing the catheter.

A sterile intravenous set can be connected to the catheter. The intravenous line can be attached to a half-filled bottle of sterile saline solution and positioned above the fluid level. Oxygen is then delivered through the bottle, below the fluid level, providing some moisture as the oxygen bubbles through the saline.

#### TRANSTRACHEAL CATHETERS

Oxygen can be administered through a jugular catheter placed with a sterile technique through the trachea. This approach is particularly useful for the emergency stabilization of animals with an upper airway obstruction. Branditz et al. (1989) have described a method for cardio-pulmonary resuscitation that can be performed by one person by administering oxygen at a high flow rate of 15 L/ min through a tracheal catheter. In this method a large jugular catheter is placed as described for transtracheal washing (see Chapter 20).

#### **ENDOTRACHEAL TUBES**

Endotracheal tubes are used to administer oxygen during surgical procedures and cardiopulmonary resuscitation. They can be used to bypass most upper airway obstructions for emergency stabilization. Pure oxygen can be administered for short periods. Longer supplementation requires the mixing of 100% oxygen with room air. Ventilation can be provided with a cuffed endotracheal tube. Trauma to the trachea is decreased through the use of high-volume, low-pressure cuffs and by inflating the cuff with the least amount of pressure necessary to create a seal. If positive-pressure ventilation is not being used, the cuff can remain deflated.

Because endotracheal tubes are not tolerated by alert animals, tracheal tubes are preferred for long-term management. Conscious animals in which endotracheal tubes are used must be given sedatives, analgesics, paralyzing agents, or a combination of these drugs. The combination of hydromorphone and diazepam is adequate in some animals. Pentobarbital, administered intravenously to effect, can be added if necessary. The combination of ketamine and valium may be safer for the initial intubation of patients that are hypoxemic. Following intubation and improvement in hypoxemia, morphine and pancuronium can be given.

The cuff should be deflated when possible to minimize tracheal damage. The tube must be cleaned periodically to remove secretions (see the recommendations for tracheal tube cleaning), and frequent flushing of the oral cavity is performed. Moisture must be added to the inspired gases, as previously discussed.

#### **TRACHEAL TUBES**

Tracheal tubes are placed through the tracheal rings and are readily tolerated by conscious animals. It is rare that an animal requires an emergency tracheostomy. Nearly all such animals can be stabilized using other techniques. Thus tracheal tubes can be placed using a careful, sterile surgical technique. Tracheal tubes are generally used for the management of animals with an upper airway obstruction. Room air often contains adequate oxygen for use in animals with an upper airway obstruction once the obstruction has been bypassed.

The tube itself should have a diameter nearly as wide as the tracheal lumen and a length of 5 to 10 rings. It is necessary to use high-volume, low-pressure cuffs to prevent tracheal damage and subsequent stricture. Double-lumen tubes are ideal for this method. The inner tube can be removed for cleaning and replaced easily. Single-lumen tubes also work and may be necessary in small animals.

Tracheal tubes are usually placed with the animal anesthetized with a short-acting agent. The trachea is exposed through a ventral midline incision made just beneath the larynx. The trachea is entered through an incision made a few rings below the cricoid cartilage, parallel to the trachea and perpendicular to the rings, and through just enough rings to allow passage of the tube. Either end of the incision can be widened with a small transverse incision. Stay sutures are placed on each side of the incision to facilitate initial placement of the tube as well as later replacement if the tube is accidentally or intentionally removed. The tube is then inserted into the opening. With minimal pressure on the airway, it is tied with gauze around the neck of the animal. Few or no sutures are used to close the incision to prevent the collection of air subcutaneously. A gauze sponge with a slit cut in it and coated with antiseptic ointment can be placed over the incision and around the tube.

The tube must be monitored for obstruction and cleaned. The inner tube of double-lumen tubes can be easily removed for this purpose. The tube is cleaned every 30 to 60 minutes initially, with the interval increased as less secretions accumulate. Sterile technique is used when handling the tubes, and they must be replaced if they become contaminated.

Single-lumen tubes are difficult to remove and replace safely for the first few days unless stay sutures are left in place. Periodic cleaning can be performed with the tube in place. Sterile saline solution is instilled into the tube for this purpose. To perform suctioning, a sterile urinary catheter with several openings at the end is attached to a suction unit and passed through the tube. The trachea and tracheal tube are then suctioned to remove secretions. Suctioning is performed for short intervals to allow the lungs to reinflate. Cleaning is performed every few hours initially, then less frequently if secretions are not accumulating.

A smaller tube can be used once the animal is able to oxygenate adequately with room air. The tube can be removed when the animal can oxygenate by breathing around a small

tube with the lumen obstructed. The incision is allowed to heal without suturing. The tip of the tube is cultured for bacteria.

Antibiotics are not administered prophylactically. Any existing infection or infections that occur during therapy are treated on the basis of culture and sensitivity information.

#### OXYGEN CAGES

Oxygen cages provide an oxygen-enriched environment with minimal stress to animals. However, the animal is isolated from direct contact, which can be a disadvantage. Other environmental factors, such as humidity, temperature, and carbon dioxide concentration, must be monitored and controlled or extreme stress and even death can occur. The animal is totally dependent on proper cage function. The ability of the cage to maintain the correct environment varies with the specific cage as well as with each animal. Commercial cages are available for veterinary use. Incubators from human hospitals can be modified for small animals.

#### **VENTILATORY SUPPORT**

The purposes of ventilatory support are to decrease the retention of carbon dioxide and to improve oxygenation. Ventilatory support is labor intensive and associated with complications, however. It is used when other means of respiratory support are not adequate.

The retention of carbon dioxide, or hypercapnia, occurs in animals that are unable to ventilate adequately. Spontaneous ventilation can be impaired by neurologic dysfunction, such as that which occurs with severe head trauma, polyneuropathies, and some toxicities. Ventilatory support is recommended in such animals if the PacO<sub>7</sub> level increases to more than 60 mm Hg. Hypoventilation caused by a pleural effusion or pneumothorax is treated by removing the fluid or air, not by positive-pressure ventilation. Hypoventilation caused by an upper airway obstruction is treated by establishing a patent airway.

Animals with cerebral edema, usually caused by trauma, may benefit from ventilatory support to maintain the PaCO<sub>2</sub> within 20 to 30 mm Hg. The resultant decrease in blood flow to the brain may decrease the total intracranial volume, thereby decreasing pressure on the brain.

Animals with severe lung disease may be unable to maintain adequate oxygenation without ventilatory support. Positive-pressure ventilation is routinely necessary for the management of patients with acute respiratory distress syndrome (ARDS; see Chapter 22, p. 319). As previously noted, the long-term administration of air with an oxygen concentration greater than 50% results in serious lung damage. If the PaO<sub>2</sub> cannot be maintained at greater than 60 mm Hg without excessive oxygen supplementation, ventilatory support is indicated.

The delivery of air by positive pressure is different from the normal inhalation of air by negative pressure. With positive pressure, the distribution of ventilation within the lungs is altered. The intrathoracic pressure increases each time the lungs are filled with air, which results in decreased venous return to the heart. Along with other effects, systemic hypotension results and can be severe enough to cause acute renal failure. Compliance of the lungs also decreases over time in animals receiving positive-pressure ventilation. As the lungs become stiffer, greater pressures are necessary to expand them. Careful monitoring of animals is essential during ventilation. Important variables to monitor include blood gas values, compliance, mucous membrane color, capillary refill time, pulse quality, arterial blood pressure, central venous pressure, lung sounds, and urine output. The extensive nursing care and monitoring required for these patients usually limit the use of long-term ventilatory support to large referral hospitals.

#### Suggested Readings

Branditz FK et al: Continuous transtracheal oxygen delivery during cardiopulmonary resuscitation: an alternative method of ventilation in a canine model, *Chest* 95:441, 1989.

Court MH et al: Inhalation therapy: oxygen administration, humidification, and aerosol therapy, Vet Clin North Am Small Anim Pract 15:1041, 1985.

Fitzpatrick RK et al: Nasal oxygen administration in dogs and cats: experimental and clinical investigations, *J Am Anim Hosp Assoc* 22:293, 1986.

McKiernan BC: Principles of respiratory therapy. In Kirk RW, editor: Current veterinary therapy VIII, Philadelphia, 1983, WB Saunders, p 216.

Moon PF et al: Mechanical ventilation. In Kirk RW et al, editors: *Current veterinary therapy XI*, Philadelphia, 1992, WB Saunders, p 98.



#### Drugs Used in Respiratory Disorders

GENERIC NAME	TRADE NAME	DOGS (mg/kg*)	CATS (mg/kg*)
Acepromazine	_	0.05 IV, IM, SC (maximum, 4 mg)	0.05 IV, IM, SC (maximum, 1 mg)
Amikacin	Amiglyde	5-10 IV, SC q8h	Same
Aminophylline	_	11 PO, IV, IM q8h	5 PO, IV, IM q12h
Amoxicillin	Amoxi-tab	22 PO q8-12h	Same
, anoxienmi	Amoxi-drop	22 10 40 12.1	came
Amoxicillin-clavulanate	Clavamox	20-25 PO q8h	Same
Ampicillin		22 PO, IV, SC q8h	Same
Ampicillin-sulbactam	Unasyn	22 mg/kg (ampicillin) IV q8h	Same
Atropine	—	0.05 SC	Same
Azithromycin	Zithromax	5-10 mg/kg PO q24h for 3 days, then q 48-72h	5-10 mg/kg PO q24h for 3 days, then q72h
Butorphanol	Torbutrol	0.5 PO q6-12h (antitussive)	Not recommended
Cefazolin	_	20-25 IM, IV q8h	Same
Cephalexin	Keflex	20-40 PO q8h	Same
Cetirizine	Zyrtec	_ qon	1 PO q24h
Chloramphenicol	_	50 PO, IV, SC q8h	10-15 PO, IV, SC q12h
Chlorpheniramine	Chlor-Trimeton	4-8 mg/dog q8-12h	2 mg/cat q8-12h
Clindamycin	Antirobe	5.5-11 PO, IV, SC q12h	Same
Cyclophosphamide	Cytoxan	50 mg/m <sup>2</sup> PO q48h	Same
Cyproheptadine	Periactin	30 mg/m 1 O q40m	2 mg/cat PO q12h
Dexamethasone	Azîum		Same
Dextromethorphan	AZIUIII	1-2 PO q6-8h	Not recommended
	— Valium	0.2-0.5 IV	Noi recommended
Diazepam		1 IM; 2-4 PO	_ Same
Diphenhydramine	Benadryl		
Doxycycline	انسان انسان	5-10 PO, IV q12h	Same
Enrofloxacin Fenbendazole (for lungworms)	Baytril Panacur	10-20 PO, IV, SC q24h 25-50 mg/kg PO q12h for 14 days	_ Same
Furosemide	lasix	2 PO, IV, IM q8-12h	Same
Glycopyrrolate		0.005 IV, SC	Same
Heparin	_	200-300 U/kg SC q8h	Same
Hydrocodone bitartrate	— Hycodan	0.25 PO q6-12h	Not recommended
Hydromorphone	—	0.05 IV, IM; can repeat IV q3min to effect; duration 2-4h	0.025-0.05 IV, IM; can repeat IV q3min to effect; stop if mydriasis occurs
Itraconazole (for	Sporanox	5 PO q12h with food	_ ′
aspergillosis)	1	•	
lvermectin	_	See text for specific parasites	See text for specific parasites
Ketamine	Ketaset Vetalar		2-5 IV
Lysine	_	_	500 mg/cat PO q12h
Marbofloxacin	Zeniquin	3-5.5 PO q24h	Same
Meropenem	Merrem IV	8 IV, SC q8h	Same
Methylprednisolone acetate	Depo-Medrol	=	10 mg/cat IM q2-4 weeks
Metronidazole	Flagyl	10 PO q8h	10 PO q12h
Milbemycin (for nasal mites)	Interceptor	0.5-1 PO q7-10d for 3 treatments	=
Morphine		O.1 IV; repeat q3min to effect; duration 1-4h	_
Oxtriphylline	Choledyl	14 PO q8h	_
Oxymetazoline 0.025%	Afrin (0.025%)	_ '	1 drop/nostril q24h for 3 days, then withhold for 3 days
Phenylephrine 0.25%	Nec-Synephrine (0.25%)	- Address	1 drop/nostril q24h for 3 days, then withhold for 3 days
Praziquantel (for Paragonimus)	Droncit	23 PO q8h for 3 days	Same



GENERIC NAME	TRADE NAME	DOGS (mg/kg*)	CATS (mg/kg*)
Prednisone	_	0.25-2 PO q12h	Same
Prednisolone sodium succinate	Solu-Delta-Cortef	Up to 10 IV	Same
Sildenafil	Viagra	0.5 q12h; increase to effect up to 2 q8h	_
Terbutaline	Brethine	1.25-5 mg/dog PO q8-12h	1/8-1/4 of 2.5-mg tablet/cat q12h PO to start; 0.01 mg/kg SC, repeat once in 5-10 min if necessary
Tetracycline	_	22 PO q8h	Same
Tetracycline ophthalmic ointment	_	- '	q4-8h
Theophylline base (immediate release)		9 PO q8h	4 PO q12h
Theophylline (long- acting formulations)†	_	10 PO q12h	15 PO q24h in evening
Trimethoprim- sulfadiazine	Tribrissen	15-30 PO q12h	Same
Vitamin K <sub>1</sub>	Mephyton Aquamephyton	2-5 PO, SC, q24h	Same
Warfarin	Coumadin	0.1-0.2 PO q24h	0.5 mg/cat

IV, Intravenous; IM, intramuscular; SC, subcutaneous; PO, by mouth.

<sup>\*</sup>Unless otherwise noted.

<sup>†</sup>Dosages are for theophylline SR (Theochron or TheoCap, Inwood Laboratories, Inwood, N.Y.). Because of differences in available products, appropriate dosages are uncertain and therapeutic monitoring of animals should be considered. See Chapter 21 for further discussion.

#### PART THREE

#### **DIGESTIVE SYSTEM DISORDERS**

Michael D. Willard

CHAPTER

# Clinical Manifestations of Gastrointestinal Disorders



#### CHAPTER OUTLINE

DYSPHAGIA, HALITOSIS, AND DROOLING DISTINGUISHING REGURGITATION FROM VOMITING FROM EXPECTORATION REGURGITATION VOMITING **HEMATEMESIS** DIARRHEA **HEMATOCHEZIA** MELENA **TENESMUS** CONSTIPATION FECAL INCONTINENCE WEIGHT LOSS **ANOREXIA** ABDOMINAL EFFUSION **ACUTE ABDOMEN** ABDOMINAL PAIN ABDOMINAL DISTENTION OR ENLARGEMENT

#### DYSPHAGIA, HALITOSIS, AND DROOLING

Dysphagia, halitosis, and drooling may co-exist in many animals with oral disease. Dysphagia (i.e., difficulty in eating) usually results from oral pain, masses, foreign objects, trauma, neuromuscular dysfunction, or a combination of these (Box 28-1). Halitosis typically signifies an abnormal bacterial proliferation secondary to tissue necrosis, tartar, periodontitis, or the oral or esophageal retention of food (Box 28-2). Drooling occurs because animals are unable to or are in too much pain to swallow (i.e., pseudoptyalism). Excessive salivation is usually due to nausea; animals that are not nauseated rarely produce excessive saliva (Box 28-3). Although any disease causing dysphagia may have an acute

onset, the clinician usually should first consider foreign objects or trauma as the cause in such an animal. The environment and vaccination history should also be assessed to determine whether rabies is a possibility.

The next step is a thorough oral, laryngeal, and cranial examination. This examination is often the most important diagnostic step because most problems producing oral pain can be partially or completely defined on the basis of physical examination findings. Ideally, this is done without chemical restraint to allow pain to be detected. However, the animal often must be anesthetized for the oral examination to be performed adequately. A search for anatomic abnormalities, inflammatory lesions, pain, and discomfort should always be made. If pain is found, the clinician should determine whether it occurs when the mouth is opened (e.g., retrobulbar inflammation), is associated with extraoral structures (e.g., muscles of mastication), or originates from the oral cavity. The clinician should also search for fractures, lacerations, crepitus, masses, enlarged lymph nodes, inflamed or ulcerated areas, draining tracts, loose teeth, excessive temporal muscle atrophy, inability to open the mouth while the animal is under anesthesia, and ocular problems (e.g., proptosis of the eye, inflammation, or strabismus suggestive of retrobulbar disease). If oral pain is apparent but cannot be localized, retrobulbar lesions, temporomandibular joint disease, and posterior pharyngeal lesions should be considered. A concurrent clinicopathologic evaluation may be useful, especially if oral examination findings indicate the presence of systemic disease (e.g., lingual necrosis resulting from uremia, chronic infection secondary to hyperadrenocorticism).

Biopsies should be done of mucosal lesions (e.g., masses, inflamed or ulcerated areas) and painful muscles of mastication. Masses that do not disrupt the mucosa, especially those on the midline and dorsal to the larynx, can be difficult to discern and are sometimes found only by careful digital palpation. Fine-needle aspiration and cytologic evaluation are reasonable first steps for the diagnosis of masses. Remember that fine-needle aspirates can only find disease; they cannot



#### Causes of Dysphagia

#### Oral Pain

Fractured bones or teeth

Trauma

Periodontitis or caries (especially cats)

Mandibular or maxillary osteomyelitis

Other causes

Retrobulbar abscess/inflammation

Various other abscesses or granulomas of the oral cavity Temporal-masseter myositis

Stomatitis, glossitis, pharyngitis, gingivitis, tonsillitis, or sialoadenitis

Immune-mediated disease

Feline viral rhinotracheitis, calicivirus, leukemia virus, or immunodeficiency virus

Lingual foreign objects, other foreign objects, or granulomas

Tooth root abscess

Uremia

Electrical cord burn

Miscellaneous causes

- Thallium
- Caustics

Pain associated with swallowing: esophageal stricture or esophagitis

#### Oral Mass

Tumor (malignant or benign) Eosinophilic granuloma Foreign object (oral, pharyngeal, or laryngeal) Retropharyngeal lymphadenomegally Inflammatory polyp of middle ear (primarily cats) Sialocele

#### **Oral Trauma**

Fractured bones (e.g., mandible, maxilla) Soft tissue laceration Hematoma

#### Neuromuscular Disease

Localized myasthenia Temporal-masseter myositis Temporomandibular joint disease Oral, pharyngeal, or cricopharyngeal dysfunction Cricopharyngeal achalasia

Tick paralysis Rabies Tetanus **Botulism** 

Various cranial nerve dysfunctions/CNS disease



BOX 28-2

#### Causes of Halitosis

#### **Bacterial Causes**

Food retained in the mouth

Anatomic defect allowing retention (exposed tooth roots, tumor, large ulcer)

Neuromuscular defect allowing retention (pharyngeal dysphagia)

Food retained in the esophagus

Tartar or periodontitis

Damaged oral tissue

Neoplasia/granuloma of mouth or esophagus Severe stomatitis/glossitis

#### **Eating Noxious Substances**

Necrotic or odoriferous food

exclude disease. Subtle masses or those dorsal to the larynx may sometimes be aspirated more accurately with ultrasonographic guidance. Multiple aspirations are usually done before a wedge or punch biopsy is performed.

Incisional biopsy specimens must include generous amounts of submucosal tissues. Many oral tumors cannot be diagnosed on the basis of findings from superficial biopsy specimens because of superficial necrosis and inflammation



BOX 28-3

#### Major Causes of Drooling

#### Ptyalism

Nausea

Hepatic encephalopathy (especially feline)

Seizure activity

Chemical or toxic stimulation of salivation (organophosphates, caustics, bitter drugs [e.g., atropine, metronidazole]] Behavior

Hyperthermia

Salivary gland hypersecretion

#### **Pseudoptyalism**

Oral pain, especially stomatitis, glossitis, gingivitis, pharyngitis, tonsillitis, or sialoadenitis (see Box 28-1)

Oral or pharyngeal dysphagia (see Box 28-1)

Facial nerve paralysis

caused by normal oral flora. Biopsies of these lesions are often not done aggressively because they bleed profusely and are hard to suture. The clinician should avoid major vessels (e.g., the palatine artery) and use silver nitrate to stop hemorrhage. It is better to have difficulty stopping hemorrhage after obtaining an adequate biopsy specimen than less difficulty stopping hemorrhage after obtaining a nondiagnostic specimen. If diffuse oral mucosal lesions are noted, search carefully for vesicles (e.g., pemphigus), and if these are found, remove them intact for histopathologic and immunofluorescent studies. If vesicles are not found, then at least two or three tissue samples representing a spectrum of new and old lesions should be submitted for analysis.

If oral examination findings are not helpful, plain oral and laryngeal radiographs are usually the best next steps. Oral cultures are rarely cost-effective because the normal oral flora makes interpretation of the results difficult. Even animals with severe halitosis or stomatitis secondary to bacterial infection rarely benefit from bacterial culture, unless there is a draining tract or abscess.

Halitosis often accompanies dysphagia, in which case it is usually more productive to determine the cause of the dysphagia. If halitosis occurs without dysphagia, the clinician should first be sure that the odor is abnormal and then check for the ingestion of odoriferous substances (e.g., feces). A thorough oral examination is still the most important test. Halitosis not attributable to an oropharyngeal lesion may be originating from the esophagus. Contrast-enhanced radiographs or esophagoscopy may reveal the presence of tumors or retained food secondary to stricture or weakness. If the history and oral examination are unrevealing except for the finding of mild-to-moderate tartar accumulation, the teeth should be cleaned to try to alleviate the problem.

Drooling is usually caused by nausea, oral pain, or dysphagia. The approach to the diagnosis of oral pain and dysphagia is described under the appropriate headings. Nausea is considered in the section on vomiting.

Dysphagic animals without demonstrable lesions or pain may have neuromuscular disease. Dysphagia of muscular origin usually results from atrophic myositis (see Chapter 31). The finding of swollen, painful temporal muscles suggests acute myositis. The combination of severe temporal-masseter muscle atrophy and difficulty opening the mouth (even when the animal is anesthetized) is suggestive of chronic temporal-masseter myositis. Biopsy of affected muscles is indicated, but the clinician must ensure that muscle tissue is retrieved; it is easy to obtain only fibrous scar tissue. It may help to have serum analyzed for antibodies to type 2M muscle fibers, a finding consistent with masticatory muscle myositis but not polymyopathy.

Neurogenic dysphagia is caused by disorders in the oral (i.e., also called *prehensile*), pharyngeal, or cricopharyngeal phases of swallowing (disorders of the latter two phases are discussed in the section on regurgitation). Rabies should always be considered, despite its relative rarity. After rabies is presumptively ruled out, cranial nerve deficits (especially deficits of cranial nerves V, VII, IX, XII) should be considered. Because the clinical signs vary depending on the nerve (or nerves) affected, a careful neurologic examination must be done.

Inability to pick up food or having food drop from the mouth while eating usually indicates a prehensile disorder. Dysphagia may be noticeable in dogs and cats with pharyngeal and cricopharyngeal dysfunction, but regurgitation is often more prominent. Dynamic contrast-enhanced radiographic studies (e.g., cinefluoroscopy or fluoroscopy) are best for detecting and defining neuromuscular dysphagia. If neuromuscular problems are seemingly ruled out by these radiographic studies, then anatomic lesions and occult causes of pain (e.g., soft tissue inflammation or infection) must be reconsidered.

### DISTINGUISHING REGURGITATION FROM VOMITING FROM EXPECTORATION

Regurgitation is the expulsion of material (i.e., food, water, saliva) from the mouth, pharynx, or esophagus. It must be differentiated from vomiting (the expulsion of material from the stomach and/or intestines) and expectoration (the expulsion of material from the respiratory tract). Historical and physical examination findings sometimes allow differentiation of these three (Table 28-1). Expectoration is generally associated with coughing at the time of the event. However, because dogs that cough and gag excessively may stimulate themselves to vomit as well, careful history taking is important. Animals that regurgitate and occasionally those that vomit may cough as a result of aspiration, but oral expulsion is not consistently correlated with coughing in these patients.

The criteria in Table 28-1 are only guidelines. Some animals that appear to be regurgitating are vomiting and vice



Aids to Differentiate Regurgitation from Vomiting\*

SIGN	REGURGITATION	VOMITING
Prodromal nausea†	No	Usually
Retching‡	No	Usuallý
Material produced		,
Food	<u>+</u>	±
Bile	No	±
Blood	± (undigested)	± (digested or undigested)
Amount of material	Any amount	Any amount
Time relative to eating	Anytime	Anytime
Distention of cervical esophagus	±	No
Dipstick analysis of material		
рH	≥7	≤5 or ≥8
Bile	No	<u>+</u>

<sup>\*</sup>These are guidelines that often help distinguish vomiting from regurgitation. However, occasional animals will require plain and/or contrast-enhanced radiographs to distinguish between the two. †May include salivation, licking lips, pacing, and an anxious expression. The owner may simply state that the animal is aware that it will soon "vomit."

<sup>‡</sup>These are usually forceful, vigorous abdominal contractions or dry heaves. This is not to be confused with gagging.

versa. If the clinician cannot distinguish between the two on the basis of the history and physical examination findings, he or she may use a urine dipstick to determine the pH and whether there is bilirubin in *freshly* "vomited" material. If the pH is 5 or less, the material has originated from the stomach and probably resulted from vomiting. If the pH is more than 7 and there is no evidence of bilirubin, this is most consistent with regurgitation. The presence of bilirubin indicates that the material has originated from the duodenum (i.e., vomiting). A positive finding of blood in the urine dipstick test is not useful.

If vomiting and regurgitation still cannot be distinguished, plain and/or contrast-enhanced radiographs will usually detect esophageal dysfunction. However, some esophageal disorders (e.g., hiatal hernia, partial stricture, partial or segmental motility defect) are easily missed unless a careful radiographic technique and/or fluoroscopy are used. Endoscopy is rarely required to detect esophageal lesions missed by imaging (e.g., esophagitis).

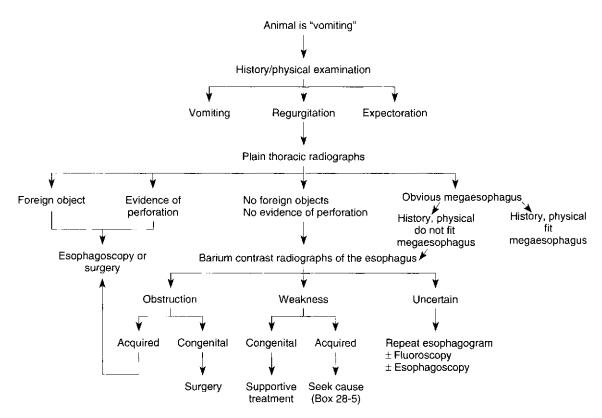
#### **REGURGITATION**

Once regurgitation is confirmed, the disease should be localized to the oral cavity/pharynx or esophagus (Fig. 28-1). The history, in combination with observation of the pet eating, should allow the clinician to detect evidence of dysphagia (e.g., undue stretching or flexing of the neck during swal-

lowing, repeated efforts at swallowing, food falling from the mouth during swallowing) if it is present. Some animals with dysphagia associated with neuromuscular disorders have more difficulty swallowing liquids than solid foods, probably because it is easier to aspirate liquids. Attempts to swallow water may produce coughing in these animals.

If a regurgitating animal is dysphagic, oral, pharyngeal, and cricopharyngeal dysfunctions should be considered; the latter two mimic each other. Fluoroscopic evaluation of swallowing during a barium meal is necessary to differentiate pharyngeal from cricopharyngeal dysfunction. If they are not accurately differentiated, inappropriate therapy may cause morbidity or mortality.

If the regurgitating animal is not dysphagic, esophageal dysfunction is most likely. The two main reasons for esophageal regurgitation are obstruction and muscular weakness. Plain thoracic radiographs, with or without barium contrast-enhancement, are the best tools for initially defining these problems. Fluoroscopy is often necessary in animals with a partial loss of peristalsis, segmental aperistalsis, gastroesophageal reflux, or sliding hiatal hernias. If the animal seems to be regurgitating but the contrast-enhanced radiographs fail to reveal esophageal dysfunction, either the assessment of regurgitation is wrong or there is occult disease (e.g., partial stricture of the esophagus, esophagitis, gastroesophageal reflux). Procedures involving the use of liquid barium sulfate may miss some lesions (e.g., partial strictures). Repeating contrast-enhanced esophagography using



**FIG 28-1**General diagnostic approach to regurgitation in the dog and cat.



#### Causes of Esophageal Obstruction

#### **Congenital Causes**

Vascular ring anomaly

Persistent fourth right aortic arch (most common type) Other vascular rings

Esophageal web (rare)

#### **Acquired Causes**

Foreign object Cicatrix/stricture

Neoplasia

Esophageal tumors

- Carcinoma
- Sarcoma caused by Spirocerca lupi
- · Leiomyoma of lower esophageal sphincter

Extraesophageal tumors

- Thyroid carcinoma
- Pulmonary carcinoma
- Mediastinal lymphosarcoma

Achalasia of the lower esophageal sphincter (very rare) Gastroesophageal intussusception (very rare)

barium plus food or performing esophagoscopy (or both) is appropriate in such patients.

Esophageal obstruction is principally caused by foreign objects and vascular anomalies, although cicatrix, tumors, and achalasia of the lower esophageal sphincter may also be responsible (Box 28-4). Obstruction should be characterized as congenital or acquired and as intraluminal, intramural, or extraesophageal. Congenital obstructions are usually extraesophageal vascular ring anomalies. Acquired intraluminal obstructions are usually caused by foreign objects or cicatrix secondary to esophagitis. The clinician should always determine whether animals with esophageal foreign objects also have a partial esophageal stricture that has predisposed them to the obstruction. Endoscopy may be both diagnostic and therapeutic in these animals; thoracotomy is seldom needed for the management of cicatrix or intraluminal foreign objects.

Esophageal weakness may be congenital or acquired. Congenital weakness is of uncertain cause, and further diagnostics are typically unfruitful. Acquired esophageal weakness usually results from an underlying neuromuscular problem. Although an underlying cause is infrequently diagnosed, finding one may lead to a permanent cure as opposed to supportive therapy, which only treats symptoms. A complete blood count (CBC), serum biochemistry profile, determination of serum antibody titers to acetylcholine receptors, an adrenocorticotropic hormone (ACTH)–stimulation test (see Chapter 53), and/or fecal examination for *Spirocerca lupi* ova are performed to look for causes of acquired esophageal weakness (Box 28-5). One may also consider searching for lead intoxication (nucleated red blood cells and basophilic stippling in the CBC, serum and urine lead concentra-



#### Causes of Esophageal Weakness

#### **Congenital Causes**

**Idiopathic** 

#### **Acquired Causes**

Myasthenia (generalized or localized) Hypoadrenocorticism

Esophagitis

Gastroesophageal reflux

- Hiatal hernia
- Anesthesia-associated reflux
- Spontaneous reflux

Foreign body

Caustic ingestion

- latrogenic (e.g., doxycycline)
- Disinfectants, chemicals, etc.

Persistent vomiting

Excessive gastric acidity

- Gastrinoma
- Mast cell tumor

Fungal organisms (e.g., pythiosis)

Myopathies/neuropathies

Miscellaneous causes

Dysautonomia

Spirocerca lupi

Dermatomyositis (principally in Collies)

**Botulism** 

Tetanus

Lead poisoning

Canine distemper

Idiopathic

tions), canine distemper (retinal lesions), and neuropathy-myopathy (electromyography, nerve biopsy, muscle biopsy). Chagas' disease causes esophageal disease in people, but it is unknown whether it causes esophageal weakness in dogs.

Esophagoscopy may detect esophagitis or small lesions (e.g., partial strictures) that contrast-enhanced esophagrams do not reveal. If esophagitis is found, the clinician should look carefully for a cause (e.g., hiatal hernia, gastric outflow obstruction). After entering the stomach, the clinician retroflexes the tip of the endoscope and examines the lower esophageal sphincter for leiomyomas. Gastroduodenoscopy is performed concurrently to look for gastric and duodenal reasons for gastroesophageal reflux or vomiting. If fluoroscopy is available, the lower esophageal sphincter should be observed for several minutes to detect the frequency and severity of gastroesophageal reflux (normal animals may show occasional reflux).

#### **VOMITING**

Vomiting is usually caused by (1) motion sickness, (2) ingestion of emetogenic substances (e.g., drugs), (3) gastrointes-



#### Causes of Vomiting

#### Motion Sickness (Acute)

#### Diet

Dietary indiscretion Dietary intolerance

#### **Emetogenic Substances (Acute)**

Drugs: almost any drug can cause vomiting (especially drugs administered orally [PO]), but the following drugs seem especially likely to cause vomiting:

Digoxin

Cyclophosphamide

Cisplatin

Dacarbazine

Doxorubicin

Erythromycin

Penicillamine

Tetracycline/doxycycline

Amoxicillin clavulanic acid

Nonsteroidal antiinflammatory drugs

Xylazine

Toxic chemicals

Strychnine

Heavy metals

#### Gastrointestinal Tract Obstruction (Acute or Chronic)

Gastric outflow obstruction

Benign pyloric stenosis

Foreign object

Gastric antral mucosal hypertrophy

Neoplasia

Nonneoplastic infiltrative disease (e.g., pythiosis)

Gastric malpositioning

- Gastric dilation or volvulus (see nonproductive retching)
- Partial gastric dilation/volvulus (does not always cause clinical signs)

#### Intestinal

Foreign object

- Nonlinear objects
- Linear objects

Neoplasia

Intussusception

Cicatrix

Torsion/volvulus

#### Gastrointestinal/Abdominal Inflammation (Acute or Chronic)

Inflammatory bowel disease

Gastritis

without ulcers/erosions

with ulcers/erosions

non-obstructing foreign body

Enteritis (acute)

**Parvovirus** 

Hemorrhagic gastroenteritis

Parasites (acute or chronic), especially Physaloptera

Pancreatitis.

Peritonitis (acute or chronic)

Colitis (acute or chronic)

#### **Extraalimentary Tract Diseases (Acute or Chronic)**

Uremia

Adrenal insufficiency

Hypercalcemia

Hepatic insufficiency or disease

Cholecystitis

Diabetic ketoacidosis

Pyometra

Endotoxemia/septicemia

#### Miscellaneous Causes (Acute or Chronic)

Dysautonomia

Feline hyperthyroidism

Postoperative nausea

Overeating

Idiopathic hypomotility

Central nervous system disease

"Limbic" epilepsy

Tumor

Meningitis

Increased intracranial pressure

Sialoadenitis/sialoadenosis\*

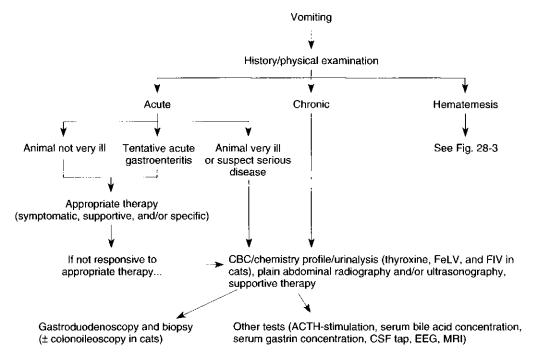
Behavior

tinal (GI) tract obstruction, (4) abdominal (especially alimentary tract) inflammation or irritation, and (5) extragastrointestinal tract diseases that may stimulate the medullary vomiting center or the chemoreceptor trigger zone (Box 28-6). Occasionally, central nervous system (CNS) disease, behavior, and learned reactions to specific stimuli may cause vomiting. If the cause of the vomiting is not apparent on the basis of the history and physical examination findings, the next step depends on whether the vomiting is acute or chronic and whether there is hematemesis (Figs. 28-2 and 28-3). Remember that blood in vomitus may be fresh

(i.e., red) or partially digested (i.e., "coffee grounds" or "dregs").

In animals with acute vomiting without hematemesis, the clinician should first search for obvious causes (e.g., ingestion of a foreign body, intoxication, organ failure, parvovirus) as well as for secondary fluid, electrolyte, or acid-base abnormalities or sepsis that require prompt, specific therapy. If the animal's condition seems stable and there is no obvious cause, symptomatic treatment is often used for 1 to 3 days. If the animal is too sick for the clinician to take a chance on guessing wrong, if the vomiting persists for 2 to 4 days after

<sup>\*</sup>It is necessary to determine whether this is the cause of vomiting or an effect of vomiting.



**FIG 28-2**General diagnostic approach to vomiting in the dog and cat. *CBC*, Complete blood count; *FeLV*, feline leukemia virus; *FIV*, feline immunodeficiency virus; *CSF*, cerebrospinal fluid; *EEG*, electroencephalogram; *MRI*, magnetic resonance imaging.

the start of symptomatic therapy, or if the condition worsens during this initial time, then more aggressive diagnostic testing is usually indicated.

The clinician should search for historical evidence of the ingestion of foreign objects, toxins, inappropriate food, or drugs. Physical examination is used to look for abdominal abnormalities (e.g., masses), linear foreign objects caught under the tongue, and evidence of extraabdominal disease (e.g., uremia, hyperthyroidism). The clinician should always consider the possibility of linear foreign bodies in vomiting cats and carefully examine the base of the tongue. Chemical restraint (e.g., ketamine HCl, 2.2 mg/kg of body weight given intravenously) may be necessary to examine this area properly. The abdomen is palpated to search for masses or pain, but even careful palpation may miss short ileocolic intussusceptions in the craniodorsal area of the abdomen. It is reasonable to perform fecal examination for parasites because they can be the cause of vomiting. If a cause cannot be found and the animal is not unduly ill, the clinician may prescribe a therapeutic trial (e.g., pyrantel and a dietary trial; see Table 30-7 and Chapter 30). Therapeutic trials should be designed so that the failure of a treatment allows the clinician to exclude at least one disease and then look for others.

If acute vomiting does not respond to symptomatic therapy or if the animal is so sick that the clinician cannot take a chance on symptomatic therapy being ineffective, aggressive diagnostic testing is indicated. Animals with acute or chronic vomiting without hematemesis should undergo abdominal imaging (i.e., radiography, ultrasonography) to look for problems such as an intestinal obstruction, foreign objects, masses, pancreatitis, peritonitis, poor serosal contrast in the region of the pancreas, free abdominal fluid, or free abdominal gas. Abdominal ultrasonography can be more revealing than plain radiographs; however, radiographs may be more sensitive in revealing some foreign bodies. A CBC, serum biochemistry profile, and urinalysis are also indicated. Cats should be tested for feline leukemia virus, feline immunodeficiency virus, and hyperthyroidism. It may be necessary to measure serum bile acid concentrations (or blood ammonia concentrations) or perform an ACTH-stimulation test (or at least resting serum cortisol concentrations) to identify hepatic or adrenal insufficiency that is not indicated by results of routine serum biochemistry profiles.

If results of the CBC, chemistry profile, urinalysis, and routine abdominal imaging are not diagnostic, the next step is usually either contrast-enhanced abdominal radiography or endoscopy plus biopsy. Endoscopy is usually more cost-effective than contrast-enhanced radiography in vomiting patients. During endoscopy the clinician should biopsy the stomach and duodenum, regardless of the gross mucosal appearance. In cats endoscopic biopsy of the ilcum and ascending colon may be required to reveal the cause of vomiting. If laparotomy is chosen over endoscopy, the entire abdomen should be examined and biopsy of the stomach, duodenum, jejunum, ileum, mesenteric lymph node, liver, and, in cats, the pancreas should be performed.

If the cause of vomiting is undiagnosed after biopsy, the basis for previously excluding the different diseases should be reviewed. Diseases may be inappropriately ruled out (or diagnosed) because the clinician does not understand the

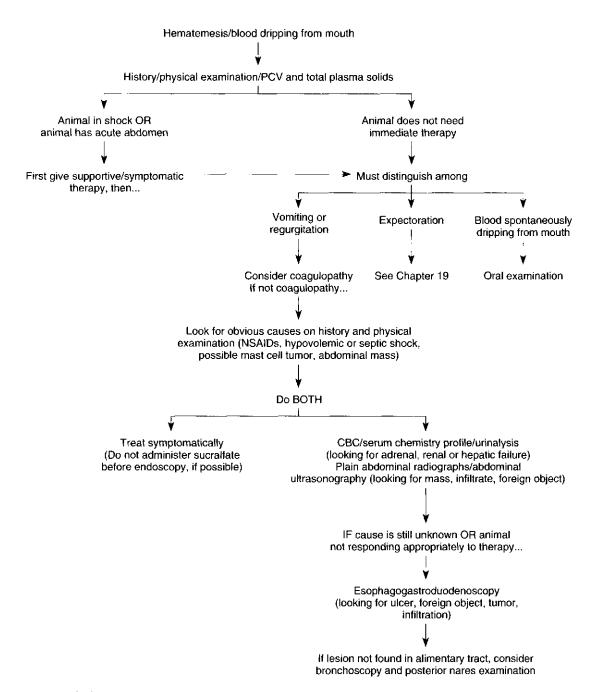


FIG 28-3
General diagnostic approach to hematemesis in the dog and cat. PCV, Packed cell volume; CBC, complete blood count.

limitations of certain tests. For example, dogs with hypoadrenocorticism may have normal electrolyte concentrations; inflammatory gastric and bowel disease may be localized to one area of the stomach or intestine and rarely causes significant changes in the white blood cell count; hyperthyroid cats may have normal serum thyroxine concentrations; dogs and cats with hepatic failure may have normal serum alanine aminotransferase and alkaline phosphatase activities; dogs and cats with pancreatitis may have normal serum amylase and lipase activities and normal abdominal ultrasound examinations; and *Physaloptera* infections are almost never diagnosed on the basis of fecal examination results. Finally, the clinician may have to consider less common diseases that are more difficult to diagnose (e.g., idiopathic gastric hypomotility, occult CNS disease, "limbic epilepsy").

#### HEMATEMESIS

The clinician must often use history and physical examination to help identify hematemesis as well as distinguish it from other problems. Hematemesis may involve expulsion of digested blood (i.e., "coffee grounds") or fresh blood. Animals with oral lesions that have blood dripping from their lips do not have hematemesis. Likewise, hemoptysis (i.e., coughing up blood) is not hematemesis.

The clinician should further distinguish vomiting that produces specks of blood from vomiting in which there is substantial blood present. The former may be caused by gastric mucosal trauma secondary to vigorous vomiting from any cause, and animals with such "hematemesis" should generally be treated as described in the previous section on vomiting. Patients that produce more substantial amounts of blood generally should be approached differently. Although hematemesis is usually caused by gastroduodenal ulceration and erosion (GUE), the clinician should not automatically start treating affected patients with antacids, cytoprotective agents, or sucralfate. Shock (e.g., hypovolemic, septic) and acute abdominal conditions should be eliminated first. The clinician should check the hematocrit and plasma total protein concentration to determine whether a blood transfusion is necessary (see Fig. 28-3). The clinician should next try to identify the cause, whether it is a coagulopathy (uncommon), the ingestion of blood from another site (e.g., the

respiratory tract), or GUE (Box 28-7). Historical and physical examination findings may help in ruling out a coagulopathy or respiratory tract disease as the cause. However, platelet counts and the clotting capability (e.g., one-stage prothrombin time, partial thromboplastin time, buccal mucosal bleeding time) are preferred. The clinician should then look for obvious causes of GUE (e.g., acute gastritis, hemorrhagic gastroenteritis [HGE], ulcerogenic drugs [e.g., nonsteroidal antiinflammatory drugs, dexamethasone], recent severe hypovolemic shock, systemic inflammatory response syndrome, abdominal masses that may involve the gastric mucosa, cutaneous mast cell tumors). It is important to remember that a mast cell tumor can grossly mimic almost any other benign or malignant neoplasm, especially lipomas.

If acute gastritis, HGE, nonsteroidal antiinflammatory drug-induced GUE, or GUE resulting from shock is strongly suspected, the clinician may elect a limited diagnostic workup (e.g., CBC, serum biochemistry panel) to define the degree of blood loss and look for evidence of renal or hepatic or adrenal failure. Then the animal can be treated symptomatically for 3 to 5 days (see pp. 407–409) to see what effect this has in controlling clinical signs. Endoscopy is not neces-



#### Coagulopathy (Uncommon)

Thrombocytopenia/platelet dysfunction

Clotting factor deficiency

Disseminated intravascular coagulation

#### **Alimentary Tract Lesion**

Gastrointestinal tract ulceration/erosion (important)

Infiltrative disease

- Neoplasia
  - Leiomyoma
  - Carcinomas
  - Lymphomas
- Pythiosis (especially younger dogs in the southeastern United States)
- Inflammatory bowel disease (uncommon)

"Stress" ulceration

- Hypovolemic shock (common)
- Septic shock (i.e., systemic inflammatory response syndrome)
- After gastric dilation or volvulus
- Neurogenic "shock"
- Extreme or sustained exertion

Hyperacidity

- Mast cell tumor
- Gastrinoma (rare)

latrogenic causes

- Nonsteroidal antiinflammatory drug (common and important)
- Corticosteroids (especially dexamethasone) (important)

Other causes

- Hepatic disease (common and important)
- Hypoadrenocorticism (uncommon but important)
- Pancreatitis (common and important)
- Renal disease (uncommon)
- Inflammatory diseases

Foreign objects (rarely a primary cause but will worsen preexisting ulceration or erosion)

#### Gastritis

Acute gastritis (common)

Hemorrhagic gastroenteritis (common)

Chronic gastritis

Helicobacter-associated disease (very questionable association with hematemesis in dogs and cats)

Gastric mucosal trauma from vigorous vomiting\*

Gastric polyps

Esophageal disease (uncommon)

Tumor

Inflammatory disease (e.g., severe esophagitis)

Тгаита

Bleeding oral lesion

Gallbladder disease (rare)

#### Extraalimentary Tract Lesion (rare)

Respiratory tract disorders

Lung lobe torsion

Pulmonary tumor

Posterior nares lesion

<sup>\*</sup>Hematemesis caused by vigorous vomiting usually consists of specks of blood as opposed to larger quantities

sarily helpful in many of these cases because it cannot reliably distinguish between ulcers that will heal with medical therapy and those that will require surgical resection. However, if the cause is unknown and especially if the vomiting or blood loss is severe or chronic, more aggressive diagnostic tests (e.g., abdominal imaging, gastroduodenoscopy) should be done (see Fig. 28-3). The stomach and duodenum should be imaged, preferably by abdominal ultrasonography with or without plain radiographs to look for alimentary tract infiltrations, foreign objects, and masses. Endoscopy is the most sensitive and specific means of finding and evaluating gastroduodenal ulcers and erosions. The principal indications for endoscopy in animals with upper GI blood loss include (a) distinguishing potentially resectable ulcers from widespread, unresectable erosions in patients with lifethreatening GI bleeding; (b) localizing ulcers when considering surgical resection; and (c) determining the cause of GUE in patients with upper GI blood loss of unknown cause. During endoscopy the clinician should generally biopsy mucosa in an effort to rule out neoplasia or inflammatory bowel disease. Abdominal exploratory surgery may be performed instead of endoscopy, but it is easy to miss bleeding mucosal lesions when examining the serosal surface; intraoperative endoscopy (i.e., endoscopic examination of the mucosal surface of the stomach and duodenum while the abdomen is opened) may be useful in finding lesions that the surgeon cannot discern from the serosal surface.

If the source of bleeding cannot be found using gastroduodenoscopy, the clinician should consider possible bleeding sites beyond the reach of the endoscope; blood being swallowed from a lesion in the mouth, posterior nares, trachea, or lungs; hemorrhage from the gallbladder; or an intermittently bleeding gastric or duodenal lesion. Endoscopy of the trachea and choana can be diagnostic in some cases.

#### DIARRHEA

Diarrhea is excessive fecal water. Fecal mucus is principally caused by large bowel disorders and is discussed in the section on chronic large bowel diarrhea. The best approach to the assessment of animals with diarrhea is to first distinguish acute from chronic problems.

Acute diarrhea is usually caused by diet, parasites, or infectious diseases (Box 28-8). Dietary problems are often detected by history; parasites by fecal examination; and infectious diseases by history (i.e., evidence of contagion or exposure), CBC, fecal enzyme-linked immunosorbent assay for canine parvoviral antigen, and the exclusion of other causes. If acute diarrhea becomes unduly severe or persistent, additional diagnostic tests are recommended. The diagnostic approach for such a patient is similar to that adopted for the assessment of animals with chronic diarrhea.

Animals with chronic diarrhea should first be examined for evidence of parasites; multiple fecal examinations looking for nematodes, *Giardia*, and *Tritrichomonas* are indicated. Next, the clinician should determine whether the diarrhea



#### Causes of Acute Diarrhea

#### Diet

Intolerance/allergy Poor-quality food

Rapid dietary change (especially in puppies and kittens) Bacterial food poisoning

#### **Parasites**

Helminths

Protozoa

Giardia

Tritrichomonas (feline)

Coccidia

#### Infectious Causes

Viral causes

Parvovirus (canine, feline)

Coronavirus (canine, feline)

Feline leukemia virus (including infections secondary to

Feline immunodeficiency virus (specifically infections secondary to it)

Various other viruses (e.g., rotavirus, canine distemper virus)

**Bacterial** causes

Salmonella spp.

Clostridium perfringens

Verotoxin-producing Escherichia coli

Campylobacter jejuni

Yersinia enterocolitica (questionable)

Various other bacteria

Rickettsial infection

Salmon poisoning

#### Other Causes

Hemorrhagic gastroenteritis

Intussusception

"Irritable bowel syndrome"

Ingestion of "toxins"

"Garbage can" intoxication (spoiled foods)

Chemicals

Heavy metals

Various drugs (antibiotics, antineoplastics, anthelmintics, antiinflammatories, digitalis, lactulose)

Acute pancreatitis (diarrhea usually modest component of clinical signs but can be major)

Hypoadrenocorticism

#### TABLE 28-2

#### Differentiation of Chronic Small Intestinal from Large Intestinal Diarrheas

SIGN	SMALL INTESTINAL DIARRHEA	LARGE INTESTINAL DIARRHEA	
Weight loss*	Expected	Rare*	
Polyphagia	Sometimes	Rare to absent	
Frequency of bowel movements	Often near normal	Sometimes very increased	
Volume of feces	Often increased	Sometimes decreased (because of the increased frequency)	
Blood in feces	Melena (rare)	Hematochezia (sometimes†)	
Mucus in feces	Uncommon	Sometimes	
Tenesmus	Uncommon (but may occur later in chronic cases)	Sometimes	
Vomiting	May be seen	May be seen	

<sup>\*</sup>Failure to lose weight or condition is the most reliable indication that an animal has large bowel disease. However, animals with colonic histoplasmosis, pythiosis, lymphoma, or similar infiltrative diseases may have weight loss despite large bowel involvement. †Hematochezia becomes much more important as a differentiating feature in animals that are losing weight. Its presence in such animals confirms the presence of large bowel involvement (either by itself or in combination with small bowel disease) despite weight loss.

originates from the small or large intestine. History is the best tool (Table 28-2). Failure to lose weight or body condition despite chronic diarrhea almost always indicates large bowel disease. Weight loss usually indicates the presence of small bowel disease, although severe large bowel diseases (e.g., pythiosis, histoplasmosis, malignancy) may cause weight loss. Animals with weight loss resulting from severe large bowel disease usually have obvious signs of colonic involvement (i.e., fecal mucus, marked tenesmus, hematochezia). If there is tenesmus, the clinician must ascertain whether it was present when the disease began; if tenesmus did not begin until late in the course, it may be due simply to perineal scalding or anal soreness resulting from chronic irritation.

Chronic small intestinal diarrhea can be categorized as maldigestion, nonprotein-losing malabsorptive disease, and protein-losing malabsorptive disease. Maldigestion is principally caused by exocrine pancreatic insufficiency (EPI) and rarely causes significant hypoalbuminemia (i.e., serum albumin concentration of 2.0 g/dl or less if the normal range is 2.5 to 4.4 g/dl). Film digestion tests for fecal trypsin activity, Sudan staining of feces for undigested fats, and fat absorption tests yield many false-negative and false-positive results. The most sensitive and specific test for EPI is measuring the serum trypsin-like immunoreactivity (TLI; see p. 388), which is indicated in dogs with chronic small intestinal diarrhea. The cPLI test may have use in diagnosing EPI, but this is not yet certain. EPI is rare in cats, but if suspected, an fTLI (feline TLI) is recommended.

Diagnosing EPI by treating the animal and evaluating its response to therapy is not recommended. If the animal has apparently responded to pancreatic enzyme supplementation, the enzymes should be repeatedly withheld and then readministered to ensure that the enzymes are responsible for resolution of the diarrhea. A false-positive diagnosis of EPI results in the unnecessary supplementation of expensive enzymes. Second, up to 15% of dogs with EPI do not respond

when enzymes are added to their diet. If EPI is incorrectly ruled out in such a case, then unnecessary endoscopies or operations often result. Antibiotic-responsive enteropathy (ARE) may be responsible for causing such a failure to respond to proper enzyme supplements and dietary changes. Therefore the clinician should definitively diagnose or rule out EPI before proceeding with other diagnostic tests or treatments.

Malabsorptive intestinal disease may be protein-losing (PLE) or nonprotein-losing (Fig. 28-4). The serum albumin concentration will usually be markedly decreased (i.e., 2.0 g/dl or less; normal, 2.5 to 4.4 g/dl) in the former but not in the latter; hypoglobulinemia may develop in patients with PLE. Diarrhea occurs only if the absorptive capacity of the colon is exceeded. Therefore a dog or cat can be losing weight because of small intestinal malabsorption and not have diarrhea (see the section on weight loss). If an animal has marked hypoproteinemia not resulting from protein-losing nephropathy, hepatic insufficiency, or skin lesions, then PLE must be the main consideration.

In patients with nonprotein-losing malabsorptive disease, the clinician may perform additional diagnostic tests (e.g., intestinal biopsy) or design therapeutic trials depending on how ill the patient is. Therapeutic trials are the best way to diagnose antibiotic responsive enteropathy (ARE) or dietary responsive disease. ARE cannot reliably be diagnosed on the basis of quantitated duodenal culture, and decreased serum cobalamin plus increased serum folate concentrations are of dubious sensitivity. However, if a therapeutic trial is performed, the clinician must be sure that it is done properly (e.g., long enough, correct dose) so that it will almost certainly succeed if the animal has the suspected disease. If the patient seems particularly ill (e.g., substantial weight loss) or if PLE is suspected, ultrasonography and intestinal biopsy are often the preferred next steps because spending 2 to 3 weeks waiting to see if a therapeutic trial will work can be disasterous if the therapy is incorrect and the disease pro-

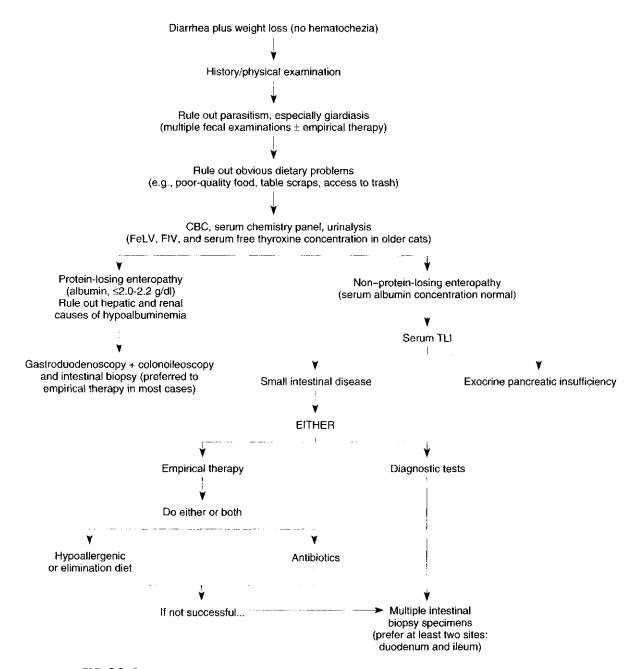


FIG 28-4
General diagnostic approach to small intestinal diarrhea in the dog and cat. CBC,
Complete blood count; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus, TLI,
trypsin-like immunoreactivity.

gresses. If diagnostic tests are chosen, abdominal imaging (especially ultrasonography) followed by gastroduodenoscopy or colonoscopy are typical next steps because the findings can help determine the cause of PLE and nonprotein-losing enteropathies in patients that do not have ARE or dietary responsive disease (Boxes 28-9 and 28-10). Absorptive tests and barium contrast—enhanced radiographs are rarely helpful. Abdominal ultrasonography may be diagnostic if it shows lymphadenopathy or intestinal infiltrates that can be aspirated percutaneously. Laparotomy or endoscopy can be performed to obtain biopsy specimens. If ultrasonog-

raphy reveals a localized lesion that cannot be reached with an endoscope, then laparotomy is necessary as opposed to endoscopy. Otherwise, endoscopy is quicker and safer than laparotomy and may allow the clinician to biopsy lesions not seen from the serosal surface. Endoscopic biopsy specimens can be nondiagnostic if the endoscopist has not been carefully trained in taking biopsy specimens. If laparotomy is performed in hypoalbuminemic animals, it may be prudent to use nonabsorbable suture material and/or perform intestinal scrosal patch grafting. The presence of distended intestinal lymphatics or lipogranulomas is suggestive of

lymphangiectasia. If a cause is not shown by intestinal biopsy specimens, the main possible reasons for this are that the specimens were inadequate (e.g., not deep enough, from the wrong place, too much artifact), the animal has occult giardiasis, the animal has ARE, the animal has a dietary intolerance, or there is localized lymphangiectasia or inflammation at a site other than the one biopsied.

Dogs with chronic large intestinal diarrhea (Box 28-11) should first undergo a digital rectal examination to search



BOX 28-9

#### Major Causes of Malabsorptive Disease

#### Dog

Dietary responsive (food intolerance or allergy; common and important)

Parasitism: giardiasis, nematodes (common and important) Antibiotic-responsive enteropathy (common and important) Inflammatory bowel disease

Neoplastic bowel disease (especially lymphoma; important but not common)

Fungal infections (regionally important)

Pythiosis

Histoplasmosis

#### Cat

Dietary responsive (food intolerance or allergy; common and important)

Parasitism: giardiasis

Inflammatory bowel disease: lymphocytic-plasmacytic enteritis (common and important)

Neoplastic bowel disease (especially lymphoma; common and important)

for mucosal thickening or proliferation. The rectum is the most common site of canine colonic neoplasia, and finding obvious mucosal lesions indicates the need for biopsy. If the rectal mucosa seems normal and the animal has not lost weight or become hypoalbuminemic (i.e., albumin <2.0 g/dl), it is often most appropriate to first try therapeutic trials.



BOX 28-10

#### Major Causes of Protein-Losing Enteropathy\*

#### Dog

Intestinal lymphangiectasia (common and important) Alimentary tract lymphoma (common and important) Severe inflammatory bowel disease

Alimentary tract fungal infections

Histoplasmosis (regionally important) Pythiosis

Chronic intussusception (especially young dogs)

Alimentary tract hemorrhage (e.g., ulceration or erosion, neoplasia, parasites)

Unusual enteropathies (e.g., chronic purulent enteropathy, severe ectasia of mucosal crypts)

Massive hookworm or whipworm infestation (regionally important)

#### Cat

Alimentary tract lymphoma
Severe inflammatory bowel disease
Alimentary hemorrhage (e.g., neoplasia, duodenal polyps, idiopathic ulceration)

\*Any gastrointestinal disease can cause protein-losing enteropathy, but these are the most common causes. Except for lymphangiectasia, these diseases do not consistently produce protein-losing enteropathy.



BOX 28-11

#### Major Causes of Chronic Large Intestinal Diarrhea

#### Dog

Dietary responsive (intolerance or allergy; important and common)

Fiber-responsive (important and common)

Functional disorder (so-called "irritable bowel syndrome")
Parasitism

Whipworms (regionally important and common)

Giardia (regionally important and common—small bowel disease that sometimes mimics large bowel disease)

Heterobilharzia (regionally important)

Bacterial diseases

"Clostridial" colitis (important and common)

Histiocytic ulcerative colitis (principally Boxers and French Bulldogs)

Fungal infections (regionally important and common)

Histoplasmosis

Pythiosis

Inflammatory bowel disease Neoplasia

Lymphoma

Adenocarcinoma

#### Ca

Dietary responsive (intolerance or allergy; important and common)

Fiber-responsive (important and common)

Functional disorder (so-called irritable bowel syndrome) Inflammatory bowel disease

Tritrichomonas

Feline leukemia virus infection (including infections secondary to it)

Feline immunodeficiency virus infection (specifically infections secondary to it)

However, multiple fecal examinations to detect whipworms, *Giardia* (a small bowel problem that can mimic large bowel disease), and *Tritrichomonas* are appropriate. Therapeutic trials usually consist of high-fiber diets, hypoallergenic diets, antibiotics to control "clostridial" colitis, or treatment for whipworms.

Additional diagnostic tests that may be done instead of therapeutic trials principally include obtaining biopsy specimens of the colonic mucosa by colonoscopy, fecal cultures, assays for clostridial toxin, and antigen tests for specific organisms (e.g., Campylobacter). Fecal cultures for specific pathogens (e.g., Salmonella spp.) should be done if the history indicates the possiblity of a contagious disorder or if the animal is not responding to seemingly appropriate therapy. Fecal cultures should be done before the animal receives enemas or intestinal lavagae solutions. Unless there is some epidemiologic reason to suspect an infectious bacteria, fecal cultures tend to be low-yield procedures that are difficult to interpret.

If the results of these tests are not diagnostic, the clinician must consider three main possibilities. First, the biopsy specimens may not be representative of the entire colonic mucosa. For example, if the disease is localized to the region of the ileocolic valve, it will be necessary to use a flexible endoscope to reach the area. Second, the pathologist may not have recognized the lesions. This occasionally happens, especially if animals have colonic histoplasmosis or neoplasia. Third, there may be no mucosal lesions. This typically occurs in animals with a dietary intolerance or allergy, "clostridial" colitis, chronic giardiasis, or irritable bowel syndrome (i.e., fiber-responsive diarrhea), all common problems in dogs.

#### HEMATOCHEZIA

If the patient has hematochezia (fresh blood in the feces) and diarrhea, the problem should usually be approached in the same way as that for animals with large bowel diarrhea (see p. 362). The patient with normal stools plus hematochezia is approached slightly differently. Streaks of blood on the outside of otherwise normal feces usually indicates the presence of a distal colonic or rectal lesion, whereas blood that is mixed into the feces suggests that bleeding is occurring higher in the colon. Coagulopathies are rarely a cause of rectal bleeding only. Focal bleeding lesions in the distal colon, rectum, or perineal region (Box 28-12) are especially important. Acute hematochezia may also result from trauma.

A thorough digital rectal examination is the best initial step (even if anesthesia is necessary). The clinician should express each anal sac repeatedly and examine the contents. If the problem is chronic and results of these tests are uninformly negative, then colonoscopy and biopsy are usually indicated. An excellent barium enema is usually inferior to a good endoscopic examination. Biopsy specimens should include the submucosa, or some neoplastic lesions will be missed. Hematochezia is rarely severe enough to cause anemia; however, a CBC can be performed to look for and evaluate the cause of anemias.

#### MELENA

Melena is caused by digested blood and is seen as coal tar black (not dark) feces. The clinician must be extremely careful to distinguish melena from stools that are intensely



BOX 28-12

Major Causes of Hematochezia\*

#### Dog

#### **Anal-Rectal Disease**

Anal sacculitis (important and common)

Neoplasia

Rectal adenocarcinoma (important)

Rectal polyp (important)

Colorectal leiomyoma or leiomyosarcoma

Perianal fistulas (important)

Anal foreign body

Rectal prolapse

Anal-rectal trauma (e.g., foreign body, thermometer, enema tube, fecal loop, pelvic fractures)

#### Colonic/Intestinal Disease

**Parasitism** 

Whipworms (important and common)

Hookworms (severe infections involving the colon)

Dietary responsive (intolerance or allergy; common) "Clostridial" colitis (common)

Hemorrhagic gastroenteritis (important)

Parvoviral enteritis (important and common)

Histoplasmosis (regionally important and common)

**Pythiosis** 

Intussusception

lleocolic

Cecocolic

Inflammatory bowel disease

Colonic trauma

Coagulopathy

#### Cat

Dietary responsive (intolerance or allergy) Inflammatory bowel disease (important) Coccidia

<sup>\*</sup>These diseases do not consistently produce hematochezia; however, when hematochezia is present, these are the most common causes.



#### Major Causes of Melena\*

#### Dog

Hookworms

Gastroduodenal tract ulceration/erosion (see Box 28-7)

Gastric or small intestinal tumor/polyp

Lymphoma

Adenocarcinoma

Leiomyoma or leiomyosarcoma

Ingested blood

Oral lesions

Nasopharyngeal lesions

Pulmonary lesions

Diet

Hypoadrenocorricism

Coagulopathies

#### Cat (Rare)

Small intestinal tumor

Lymphoma

Duodenal polyps

Other tumors (adenocarcinoma, mast cell tumor)

Coagulopathies: vitamin K deficiency (intoxication or result

ing from malabsorption)

dark green. Melena is strongly suggestive of upper alimentary tract bleeding or the ingestion of blood (Box 28-13). However, a lot of blood must enter the GI tract in a short time to produce melena, which is why most animals with upper GI hemorrhage do not have melena. A CBC is indicated to look for iron deficiency anemia (i.e., microcytosis, hypochromasia, thrombocytosis). Measuring the total serum iron concentration and the total iron-binding capacity plus staining the bone marrow for iron are more definitive tests for iron deficiency anemia. Ultrasonongraphy is very useful when looking for infiltrated, bleeding lesions (e.g., an intestinal tumor). Gastroduodenoscopy is the most sensitive test for GUE (which is often missed by ultrasonography). If gastroduodenoscopy is nonrevealing, then contrast-enhanced radiography may detect small intestinal lesions beyond the reach of the endoscope. If imaging reveals a lesion beyond the reach of the endoscope, exploratory laparotomy is required. The clinician may elect to perform exploratory surgery immediately, but it is easy to miss bleeding mucosal lesions when examining the serosa or palpating the bowel. Intraoperative endoscopy may be helpful if surgery is performed but no lesion is detected.

#### **TENESMUS**

Tenesmus (i.e., ineffectual or painful straining at urination or defecation) and dyschezia (i.e., painful or difficult elimi-



BOX 28-14

Major Causes of Tenesmus and/or Dyschezia

#### Dog

Perineal inflammation or pain: anal sacculitis

Rectal inflammation/pain

Perianal fistulae

Tumor

Proctitis (either primary disease or secondary to diarrhea

or prolapse)

Histoplasmosis/pythiosis

Colonic/rectal obstruction

Rectal neoplasia

Rectal granuloma

Perineal hernia

Constipation

Prostatomegaly

Pelvic fracture

Other pelvic canal masses

Rectal foreign object

#### Cat

Urethral obstruction

Rectal obstruction

Pelvic fracture

Perineal hernia

Constipation

Abscess near rectum

nation of feces from the rectum) are principally caused by obstructive or inflammatory distal colonic or urinary bladder or urethral lesions (Box 28-14). Colitis, constipation, perineal hernias, perianal fistulas, prostatic disease, and cystic/ urethral disease are the most common causes of tenesmus. Most rectal masses and strictures cause hematochezia; however, some do not disrupt the colonic mucosa and cause only tenesmus.

The first goal (especially in cats) is to distinguish lower urinary tract from alimentary tract disease. In cats tenesmus secondary to a urethral obstruction is often misinterpreted as constipation. By observing the animal, the clinician may be able to determine whether the animal is attempting to urinate or defecate. The clinician palpates the bladder (a distended urinary bladder indicates an obstruction; a small, painful bladder indicates inflammation); performs a urinalysis; and, if necessary, catheterizes the urethra to determine whether it is patent.

If the clinician suspects tenesmus resulting from alimentary tract disease, he or she should palpate the abdomen and rectum and visualize the anus and perineal areas. The clinician should not assume that constipation, if present, is causing the tenesmus. Severe pain (e.g., that resulting from proctitis) may make the animal refuse to defecate and cause secondary constipation. Most strictures, perineal hernias, masses, enlarged prostates, pelvic fractures, and rectal tumors can be detected during a digital rectal examination. The

<sup>\*</sup>These diseases do not consistently produce melena; however, if melena is present, these are the most common causes.

clinician may need to use two fingers to detect partial strictures when examining large dogs. Perianal fistulae are usually visible but may be detected only as perirectal thickenings. Next, the clinician expresses the anal sacs and examines their contents. Finally, the clinician evaluates the feces to determine whether they are excessively hard or have abnormal contents (e.g., hair, trash).

A biopsy should be done of any mass, stricture, or infiltrative lesion found by rectal examination. A rectal scraping is sometimes sufficient (e.g., histoplasmosis), but biopsy specimens that include the submucosa are usually preferred. Fine-needle aspiration should be performed on extracolonic masses because abscesses occasionally occur in extracolonic locations.

If the clinician is confused by the findings from a physical examination, observing the animal defecate may help define the underlying process. Animals with inflammation often continue to strain after defecating, whereas a constipated animal strains before feces are produced. Tenesmus that occurs when an animal is in a squatting position often results from colitis, whereas tenesmus that occurs when an animal is in a semiwalking or partial squatting position usually results from constipation.

#### CONSTIPATION

Constipation (the infrequent and difficult evacuation of feces) and obstipation (intractable constipation) have several causes (Box 28-15). The initial use of symptomatic therapy is often successful, but it is also important to look for causes because some problems may become harder to treat if symptomatic therapy masks the signs while the underlying disease progresses.

A search of the history for iatrogenic, dietary, environmental, or behavioral causes should be done. Feces should be examined to determine whether they contain plastic, bones, hair, popcorn, or other such material. Physical and rectal examinations are done to search for rectal obstruction or infiltration. Plain pelvic radiographs can help show whether the animal has anatomic abnormalities or a previously undetected colonic obstruction (e.g., prostatomegaly, enlarged sublumbar lymph node). Ultrasonography is the preferred technique when looking for infiltrates. A serum biochemistry panel may reveal causes of colonic inertia (e.g., hypercalcemia, hypokalemia, hypothyroidism).

Colonoscopy is indicated if the clinician suspects an obstruction too orad to be detected by digital examination.



BOX 28-15

#### Causes of Constipation

#### latrogenic Causes

Drugs

Opiates

Anticholinergics

Carafate (sucralfate)

Barium

#### Behavioral/Environmental Causes

Change in household/routine Soiled litter box/no litter box House training Inactivity

#### Refusal to Defecate

Behavioral

Pain in rectal/perineal area (see Box 28-14)

Inability to assume position to defecate

Orthopedic problem Neurologic problem

#### **Dietary Causes**

Excessive fiber in dehydrated animal

Abnormal diet

Наіг

**Bones** 

Indigestible material (e.g., plants, plastic)

#### **Colonic Obstruction**

**Pseudocoprostasis** 

Deviation of rectal canal: perineal hernia

Intraluminal and intramural disorders

Tumor

Granuloma

Cicatrix

Rectal foreign body

Congenital stricture

Extraluminal disorders

Tumor

Granuloma

**Abscess** 

Healed pelvic fracture

Prostatomegaly

Prostatic or paraprostatic cyst Sublumbar lymphadenopathy

#### Colonic Weakness

Systemic disease

Hypercalcemia

Hypokalemia

Hypothyroidism

Localized neuromuscular disease

Spinal cord trauma

Pelvic nerve damage

Dysautonomia

Chronic, massive dilation of the colon causing irreversible stretching of the colonic musculature

#### Miscellaneous Causes

Severe dehydration

Idiopathic megacolon (especially cats)

Ultrasound-guided fine-needle aspiration of infiltrative colonic lesions sometimes yields diagnostic findings, but colonoscopy (especially rigid) allows a more reliable biopsy specimen to be obtained. If a thorough diagnostic workup fails to identify a cause in a patient with a grossly dilated colon, idiopathic megacolon may be present.

#### FECAL INCONTINENCE

Fecal incontinence is caused by neuromuscular disease (e.g., cauda equine syndrome, lumbosacral stenosis) or a partial rectal obstruction. Severe irritative proctitis may cause urge incontinence. Animals with rectal obstructions continually try to defecate because the anal canal is filled with feces. Proctitis is suspected on the basis of rectal examination findings and confirmed by proctoscopy and biopsy findings. Neuromuscular disease is suspected if an abnormal anal reflex is found, usually in conjunction with other neurologic defects in the anal, perineal, hindlimb, or coccygeal region. Defects in the coccygeal region are discussed in Chapter 70.

#### **WEIGHT LOSS**

Weight loss is usually caused by one of several categories of problems (Box 28-16). If other problems with more defined lists of differentials (e.g., ascites, vomiting, diarrhea, polyuria/polydipsia) are also present, they should usually be investigated first because it may be easier to find the cause. If there are no such concurrent problems that allow relatively prompt localization of the disease, the clinician should then determine what the animal's appetite was when the weight loss began (Fig. 28-5). Almost any disease can cause anorexia. Weight loss despite a good appetite usually indicates maldigestion, malabsorption, or excessive utilization (e.g., hyperthyroidism, lactation) or inappropriate loss (e.g., diabetes mellitus) of calories.

The animal's history should be reviewed for evidence of dietary problems, dysphagia, regurgitation, vomiting, or increased use of calories (e.g., lactation, work, extremely cold temperature). Signalments suggestive of particular diseases (e.g., hyperthyroidism in older cats, hepatic failure in younger dogs with signs of portosystemic shunts) should be recognized. It is important to remember that diarrhea may be absent in animals with severe small intestinal disease.

Physical examination is performed to identify abnormalities that might help localize the problem to a particular body system (e.g., nasal disease preventing normal olfaction, dysphagia, arrhythmia suggestive of cardiac failure, weakness suggestive of neuromuscular disease, abnormally sized or shaped organs, abnormal fluid accumulations). Retinal examination may identify inflammatory or infiltrative diseases, especially in cats.

A CBC, serum biochemistry profile, and urinalysis should be done next to search for evidence of inflammation, organ



#### Causes of Weight Loss

#### Food

Not enough (especially if there are multiple animals)
Poor quality or low caloric density
Inedible

Anorexia (see Box 28-17)

Dysphagia (see Box 28-1)

**Regurgitation/Vomiting** (i.e., losing enough calories to account for weight loss; see Boxes 28-4 to 28-6)

#### Maldigestive Disease

Exocrine pancreatic insufficiency (usually but not always associated with diarrhea)

#### Malabsorptive Disease (see Box 28-9)

Small intestinal disease (may be associated with normal stools)

#### Malassimilation

Organ failure Cardiac failure Hepatic failure Renal failure Adrenal failure

#### Cancer Cachexia

#### **Excessive Utilization of Calories**

Lactation Increased work Extremely cold environment Pregnancy

Increased catabolism resulting from fever/inflammation Hyperthyroidism

#### **Increased Loss of Nutrients**

Diabetes mellitus Protein-losing nephropathy Protein-losing enteropathy

#### Neuromuscular Disease

Lower motor neuron disease

failure, or a paraneoplastic syndrome. Cats should be tested for circulating feline leukemia virus antigen and antibodies to feline immunodeficiency virus. Serum  $T_4$  (and sometimes  $fT_4$ ) concentrations should be determined in middle-aged to older cats. If clinical pathology data are not helpful, imaging is usually the next step. Thoracic radiographs (ventrodorsal and both lateral views) are important because significant thoracic disease cannot be ruled out on the basis of physical examination findings alone. Most cats and some dogs can be palpated well enough that abdominal radiographs are not cost-effective early in the workup. However, abdominal ultrasonography may reveal focal or infiltrative lesions that

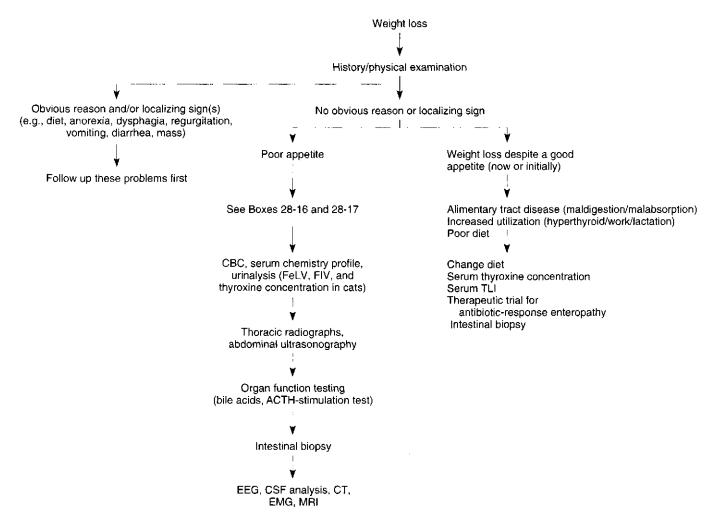


FIG 28-5

General diagnostic approach to weight loss in the dog and cat. CBC, Complete blood count; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; ACTH, adrenocorticotropic hormone; EEG, electroencephalography; EMG, electromyography; CT, computed tomography; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

cannot be palpated (plain radiographs reveal such lesions less frequently).

If the cause of weight loss remains unknown after these steps have been taken, additional tests are necessary. Daily physical examinations can be an important means of localizing the problem. Fever of unknown origin may be noted (see Chapter 90). Organ function testing (e.g., serum bile acid concentrations, ACTH–stimulation testing, serum TLI, serum cobalamin) is reasonable. Likewise, if serum  $T_4$  concentrations are normal in a cat with suspected hyperthyroidism, the serum  $fT_4$  concentration should be determined or other tests (e.g., nuclear scintigraphy) performed (see Chapter 51).

If the cause of weight loss still remains undiagnosed, the clinician should consider performing gastric and intestinal biopsy (preferably endoscopically). If a laparotomy is performed instead, the entire abdomen should be examined, multiple biopsy samples of the alimentary tract obtained, and biopsy of the liver and mesenteric lymph nodes done. Biopsy of the pancreas should also be done in cats.

Other possible diagnostic tools include tests to evaluate the CNS (i.e., cerebrospinal fluid analysis, electroencephalography, computed tomography, magnetic resonance imaging; animals that are anorectic as a result of severe CNS disease do not always have obvious cranial nerve deficits or seizures) and peripheral nerves and muscles (i.e., electromyography, muscle or nerve biopsies; sometimes the weakness associated with neuropathies and myopathies is mistaken for lethargy). (See Chapter 64.) If the cause of the weight loss still remains undiagnosed and the history and physical examination findings are still noncontributory, occult cancer becomes a major differential diagnosis. In such cases, the clinician may have to wait and retest later with the hope that the disease will progress enough to be detected.

Causes of weight loss that can be particularly difficult to diagnose include gastric disease that does not cause vomiting, intestinal disease that does not cause vomiting or diarrhea, hepatic disease with normal serum alanine aminotransferase or alkaline phosphatase activities, occult inflammatory disease, hypoadrenocorticism with normal serum electrolyte concentrations, occult cancer, "dry" feline infectious peritonitis, and CNS disease without cranial nerve deficits or seizures.

#### **ANOREXIA**

The approach to the diagnostic evaluation of animals with anorexia of uncertain cause is similar to that for animals with weight loss (see Fig. 28-5), and the differential diagnoses are also similar (Box 28-17). Inflammatory disease is often detected by the CBC or the finding of fever (see Chapter 90). GI disease may produce anorexia without vomiting or diarrhea. Cancer cachexia (with anorexia as the predominant sign) may stem from relatively small tumors that are not grossly detectable, although this is rare. Finally, CNS disease must be considered whenever there is altered mentation. However, altered mentation may resemble the depression and lethargy commonly seen in animals with other diseases.



BOX 28-17

Major Causes of Anorexia

#### Inflammatory Disease

**Bacterial** infections

Viral infections

Fungal infections

Rickettsial infections

Protozoal infections

Sterile inflammation

Immune-mediated disease

Neoplastic disease

Necrosis

**Pancreatitis** 

Fever of unknown origin

#### **Alimentary Tract Disease**

Gastric or intestinal disease

Dysphagia (especially resulting from pain)

Nausea (stimulation of the medullary vomiting center for any reason, even if it is not sufficient to cause vomiting, especially gastric or intestinal disease; see Box 28-6)

#### Metabolic Disease

Organ failure (e.g., kidney, adrenal, liver, heart)

Hypercalcemia

Diabetic ketoacidosis

Hyperthyroidism (usually causes polyphagia, but some cats have apathetic hyperthyroidism)

#### Central Nervous System Disease

Cancer Cachexia

Anosmia

**Psychologic Causes** 

#### **ABDOMINAL EFFUSION**

Abdominal effusion is usually caused by hypoalbuminemia, portal hypertension, or peritoneal inflammation. Effusions resulting from alimentary tract disorders are primarily caused by PLE or alimentary tract rupture (i.e., septic peritonitis). Some animals with PLE have normal stools, with ascites being the presenting complaint. Malignant tumors may obstruct lymphatic flow or increase vascular permeability, causing modified transudates to form or nonseptic peritonitis to develop. Modified transudates usually result from hepatic or cardiac disease or from malignant conditions. For further information on abdominal effusions, see Chapters 35 and 36.

#### **ACUTE ABDOMEN**

Acute abdomen refers to various abdominal disorders producing shock (hypovolemic or septic), sepsis, or severe pain (Box 28-18). Causes may include alimentary tract obstruction or leakage, vascular compromise (e.g., congestion, torsion, volvulus, ischemia), inflammation, neoplasia, or sepsis. The diagnostic evaluation of this problem is determined by the severity of the clinical signs (Fig. 28-6).

Shock and gastric dilation or volvulus (GDV) must be identified and treated immediately. Once these conditions are climinated, the next major decision is whether to perform exploratory surgery or initiate medical therapy. Animals with abdominal masses, foreign objects, bunched-up loops of painful small intestine (e.g., linear foreign body), or spontaneous septic peritonitis should typically undergo surgery as soon as supportive therapy has made the risk of anesthesia acceptable. If the cause of the acute abdomen is uncertain, it can be difficult to determine whether surgery is indicated. Surgery is not necessarily beneficial and may even be detrimental to animals with conditions such as pancreatitis, parvoviral enteritis, pyelonephritis, or prostatitis. Typically, abdominal imaging (i.e., plain abdominal radiography or ultrasonongraphy) and clinical pathologic studies (i.e., CBC, chemistry panel) should be performed before a laparotomy is performed. Ultrasound can reveal changes (e.g., infiltration) that radiographs cannot detect, sometimes allowing diagnosis via aspiration (and potentially eliminating the need for surgery). However, radiographs occasionally detect lesions (e.g., small foreign bodies) that were missed ultrasonographically. Imaging may reveal spontaneous pneumoperitoneum, abdominal masses, foreign objects, alimentary tract obstruction, gastric or mesenteric torsion (these require surgical treatment), or free peritoneal fluid (this requires abdominocentesis and fluid analysis for management). A barium series is seldom needed and may complicate later therapy/surgery.

If optimal medical therapy is being given and the animal's condition is clearly deteriorating or does not improve after 2 to 5 days of therapy, or if the animal continues to have excruciating pain, it is often appropriate to recommend exploratory surgery. Inform the client that you may discover



### Major Causes of Acute Abdomen

### Septic Inflammation

Septic peritonitis

Perforated gastric ulcer (NSAIDs, tumor) (important)
Perforated intestines (tumor, post-op dehiscence, linear foreign body, severe inflammation) (important and common)

Devitalized intestines (intussusception, thrombosis/infarct) Ruptured gallbladder due to septic cholecystitis or mucocoele

Abscess/Infection

- Splenic
- Hepatic
- Cholecystitis
- Prostatic
- Renal

Pyometra (ruptured)

### **Nonseptic Inflammation**

Pancreatitis (important and common)

Uroabdomen (important)

**Pansteatitis** 

#### **Organ Distention or Obstruction**

Gastric dilation or volvulus (important and common)
Intestinal obstruction resulting from many causes (important and common)

Intussusception (important)

Dystocia

Mesenteric volvulus (rare) Incarcerated obstruction (rare)

#### Ischemia

Torsion of spleen, liver lobe, testicle, or other organ Thromboembolism of abdominal organ(s)

## Other Causes of Abdominal Pain (see Box 28-19)

### **Abdominal Hemorrhage**

Abdominal neoplasia (hemangiosarcoma, hepatocellular carcinoma; important and common)

Trauma

Coagulopathy (important)

### **Abdominal Neoplasia**



BOX 28-19

### Causes of Abdominal Pain

#### **Poor Palpation Technique**

### Musculoskeletal System (Mimics Abdominal Pain)

Fractures

Intervertebral disk disease (important and common)

Diskospondylitis (important)

Abscesses

#### Peritoneum

Peritonitis

Septic (important and common)

Nonseptic (e.g., uroabdomen; important)

Adhesions (rare)

### **Gastrointestinal Tract**

Gastrointestinal ulcer

Foreign object (especially linear)

Neoplasm

Adhesions (rare)

Intestinal ischemia (rare)

Intestinal spasm (rare)

See also Box 28-18, under Organ Distention or Obstruction

### **Hepatobiliary Tract**

**Hepatitis** 

Cholelithiasis or cholecystitis

### **Pancreas**

Pancreatitis (important and common)

### Spleen

Torsion (rare)

Rupture

Neoplasm Infection (rare)

### **Urogenital System**

Pyelonephritis (important)

Lower urinary tract infection

Prostatitis (common)

Nonseptic cystitis (common in cats)

Cystic or ureteral obstruction or rupture (common, especially after trauma)

Urethritis or obstruction (common)

Metritis

Uterine torsion (rare)

Neoplasm

Testicular torsion (rare)

Mastitis (does not cause true abdominal pain but mimics abdominal pain)

### Miscellaneous Causes

Postoperative pain (especially if animal has a tight suture line)

latrogenic causes

Misoprostol

Bethanechol

Adrenalitis (associated with hypoadrenocorticism; rare)

Heavy metal intoxication (rare)

Vasculopathy (rare)

Rocky Mountain spotted fever vasculitis

Infarct

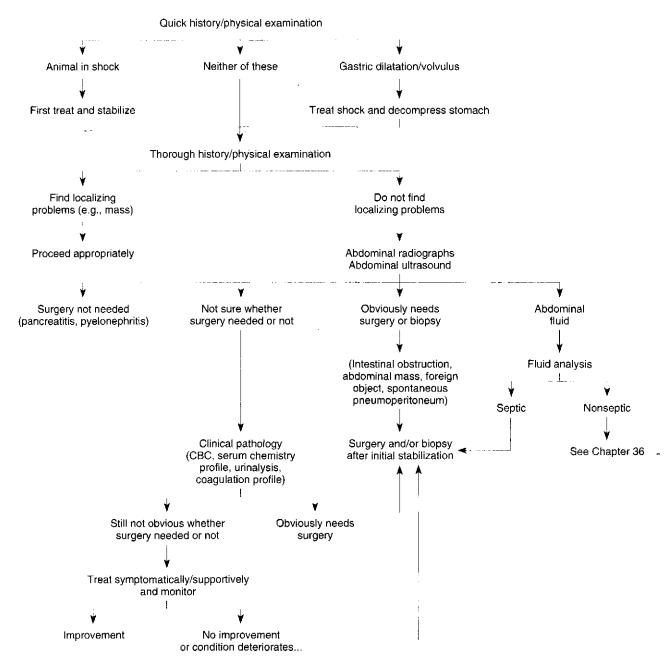


FIG 28-6
General diagnostic approach to acute abdomen in the dog and cat. CBC, Complete blood count.

the animal has a disorder not surgically correctable (especially pancreatitis) or that nothing abnormal may be found. In the latter case, the clinician should biopsy various abdominal organs and then treat the animal's symptoms while awaiting biopsy results.

### ABDOMINAL PAIN

"Abdominal" pain must first be determined to be abdominal and not extraabdominal in origin (e.g., thoracolumbar pain is often erroneously assessed as being abdominal in origin).

An animal with true abdominal pain may show obvious discomfort (e.g., it paces or repeatedly assumes different positions, repeatedly looks at or licks its abdomen) and may whine, growl, or snap if the abdomen is touched. Some dogs stretch out and assume a "praying" position (i.e., the "position of relief"). Other animals have inconspicuous signs (e.g., the animal grunts or tries to walk away when palpated, the abdomen is tensed) that are easily missed. On the other hand, a poor or rough abdominal palpation technique in normal animals may elicit a guarding response that can mimic abdominal pain. The main causes of abdominal pain are listed in Box 28-19.



### Causes of Abdominal Enlargement

#### Tissue

Pregnancy

Hepatomegaly (infiltrative or inflammatory disease, lipidosis, neoplasia)

Splenomegaly (infiltrative or inflammatory disease, neoplasia, hematoma)

Renomegaly (neoplasia, infiltrative disease, compensatory hypertrophy)

Miscellaneous neoplasia Granuloma (e.g., pythiosis)

#### Fluid

Contained in organ(s)

Congestion resulting from torsion, volvulus, or right-sided heart failure

Spleen Liver

Cysts

Paraprostatic cyst

Perinephric cyst Hepatic cyst

Hydronephrosis

Intestines or stomach (resulting from obstruction or ileus)

Pyometra

Free in abdomen

Transudate, modified transudate, exudate, blood, chyle

#### Gas

Contained in organ(s)

Stomach (gastric dilation or volvulus)

Intestines (resulting from obstruction)

In parenchymatous organs (e.g., liver) resulting from infection with gas-producing bacteria

Free in abdomen

latragenic (after laparoscopy or laparotomy)
Alimentary tract or female reproductive tract rupture

Bacterial metabolism (peritonitis)

### Fat

Obesity Lipoma

### Weak Abdominal Muscles

Hyperadrenocorticism

Faces

If the patient has abdominal pain, the goal is to determine the source. If the pain is originating from within the abdominal cavity, the diagnostic approach depends on its severity, the progression of disease, and whether there are any obvious causes. The steps taken in diagnosing the cause of abdominal pain are similar to those taken in an animal with acute abdomen. Some causes of abdominal pain can be difficult to diagnose (e.g., acute pancreatitis, localized peritonitis).

# ABDOMINAL DISTENTION OR ENLARGEMENT

Abdominal distention or enlargement may be associated with an acute abdomen, but these conditions are typically separate problems. It is best to believe clients who claim there is abdominal enlargement until good cause is found to do otherwise. There are six main causes of abdominal distention (Box 28-20).

The first concern is whether an acute abdomen is present (e.g., GDV, septic peritonitis, hemoabdomen plus shock). After an acute abdomen is ruled out, it should be possible to classify the enlargement on the basis of the physical examination and abdominal imaging (i.e., radiography or ultrasonography) findings, according to the criteria in Box 28-20. Obesity and pregnancy should be obvious. Specimens of free abdominal fluid should be obtained and analyzed as described in Chapter 36. Biopsy should be performed

on abdominal masses and enlarged organs, unless there is a reason not to (e.g., hepatomegaly caused by severe rightsided heart failure). Fine-needle aspiration is usually safe, although the leakage of septic contents or implantation of neoplastic cells may occur. Ultrasonography helps determine the potential for hemorrhage or leakage (e.g., cyst, mass with ultrasonographic characteristics of hemangiosarcoma). The finding of a spontaneous pneumoperitoneum suggests alimentary tract rupture or septic peritonitis and is an indication for immediate surgical exploration. A hollow viscus dilated with gas may indicate obstruction (i.e., gastric dilation, intestinal obstruction) or physiologic ileus (see pp. 384 and 436; Figs. 29-5 and 32-4). Surgery is indicated if an obstruction seems likely. If abdominal musculature weakness is suspected, the clinician should test for hyperadrenocorticism. Results of a CBC, serum biochemistry panel, and urinalysis are used to look for specific organ involvement (e.g., hyperadrenocorticism). Contrast-enhanced alimentary or urinary tract radiographs may be useful in selected cases, although ultrasonography often makes such techniques unnecessary.

# **Suggested Readings**

Harkin KR: Constipation, tenesmus, dyschezia, and fecal incontinence. In Ettinger SJ et al, editors: *Textbook of veterinary internal medicine*, ed 6, Philadelphia, 2005, WB Saunders.

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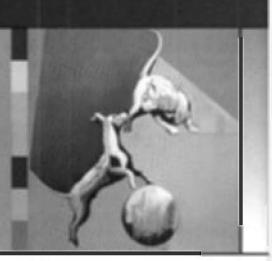
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# CHAPTER

# Diagnostic Tests for the Alimentary Tract



# CHAPTER OUTLINE

PHYSICAL EXAMINATION
ROUTINE LABORATORY EVALUATION

Complete Blood Count Coagulation

Serum Biochemistry Profile

Urinalysis

FECAL PARASITIC EVALUATION

FECAL DIGESTION TESTS

MISCELLANEOUS FECAL ANALYSES

BACTERIAL FECAL CULTURE

CYTOLOGIC EVALUATION OF FECES

RADIOGRAPHY OF THE ALIMENTARY TRACT

ULTRASONOGRAPHY OF THE ALIMENTARY TRACT IMAGING OF THE ORAL CAVITY, PHARYNX, AND

**ESOPHAGUS** 

Indications

Indications for Imaging of the Esophagus

IMAGING OF THE STOMACH AND SMALL

INTESTINE

Indications for Radiographic Imaging of the Abdomen without Contrast Media

Indications for Ultrasonography of the Stomach and Small Intestines

Indications for Contrast-Enhanced Gastrograms

Indications for Contrast-Enhanced Studies of the Small Intestine

Indications for Barium Contrast Enemas

PERITONEAL FLUID ANALYSIS

DIGESTION AND ABSORPTION TESTS

SERUM CONCENTRATIONS OF VITAMINS

OTHER SPECIAL TESTS FOR ALIMENTARY TRACT
DISEASE

**ENDOSCOPY** 

BIOPSY TECHNIQUES AND SUBMISSION

Fine-Needle Aspiration Biopsy

**Endoscopic Biopsy** 

Full-Thickness Biopsy

# PHYSICAL EXAMINATION

Routine physical examination is the first step in evaluating animals with alimentary tract disease, although oral examination is sometimes skipped in uncooperative animals. If oral, abdominal, or rectal disease is a major concern and the patient refuses to allow examination of the area, it is reasonable and appropriate to sedate or anesthetize the patient to examine and palpate this area. A common example of this is a vomiting cat with a possible linear foreign body lodged under the tongue; the clinician must thoroughly examine the mouth, even if it requires chemical restraint.

The clinician should methodically identify individual organs during abdominal palpation. In dogs the small intestine, large intestine, and urinary bladder can usually be found (unless there is an abdominal effusion, abdominal pain, or obesity). In cats both kidneys are usually palpable. In both species the clinician can usually detect substantial splenomegaly, hepatomegaly, intestinal or mesenteric masses, and intestinal foreign objects. Abdominal pain may be subtle; some animals will cry out during gentle palpation, whereas many just tense their abdomen (i.e., guarding) or try to move away. A rough palpation technique can cause a normal animal to tense up or vocalize during palpation, mimicking the reaction of an animal with abdominal pain. Light, careful palpation permits the definition of as much of the internal abdominal contents as possible. If sufficient abdominal fluid is present to prevent meaningful abdominal palpation, ballottement of the abdomen should produce a fluid wave.

During a rectal examination, the examiner should be able to identify and evaluate the colonic mucosa, anal sphincter, anal sacs, pelvic canal bones, muscular support for the rectum, urogenital tract, and luminal contents. However, it is particularly easy to misinterpret mucosal polyps as mucosal folds and to miss partial strictures that are large enough to allow a single digit to pass through easily.

# **ROUTINE LABORATORY EVALUATION**

### **COMPLETE BLOOD COUNT**

Complete blood counts (CBCs) are especially important in animals at risk for neutropenia (e.g., parvoviral enteritis, severe sepsis), infection (e.g., aspiration pneumonia), or anemia (e.g., pale mucous membranes, melena, hematemesis) and also in those that have fever, weight loss, or anorexia resulting from an occult cause. The clinician should always evaluate absolute numbers of the different types of white blood cells (WBCs), not the percentages, because an animal may have an abnormal percentage of a particular WBC and yet have a normal absolute number of cells (and vice versa). If the animal is anemic, the clinician should evaluate the CBC for evidence of iron deficiency (e.g., hypochromasia, microcytosis, thrombocytosis, increased red blood cell distribution width).

### COAGULATION

A platelet count is important. Platelet numbers can be estimated on the basis of correctly made blood smears (i.e., a dog should have an average of 8 to 30 platelets per oil immersion field; finding 1 platelet per field suggests a platelet count of approximately 15,000 to 20,000/µl). Coagulation panels may detect unsuspected coagulopathies (e.g., disseminated intravascular coagulation). Activated clotting times are crude estimates of the intrinsic clotting pathway; partial thromboplastin times are more sensitive. Mucosal bleeding time is an excellent screening test for coagulopathies severe enough to cause clinical bleeding.

### SERUM BIOCHEMISTRY PROFILE

Serum biochemistry profiles that include alanine transaminase and alkaline phosphatase activities, as well as the blood urea nitrogen, creatinine, total protein, albumin, sodium, potassium, chloride, total CO<sub>2</sub>, cholesterol, calcium, phosphorus, magnesium, bilirubin, and glucose concentrations, are important in animals with severe vomiting, diarrhea, ascites, unexplained weight loss, or anorexia. These values are crucial to correctly diagnosing the animal's problem and appropriately treating it. The clinician cannot predict the changes that will occur or the magnitude of the changes in a particular animal, even when the cause of the disease is known. The total carbon dioxide concentration is not as definitive as blood gas analysis but helps define the acid-base status, which also cannot be accurately predicted.

The albumin concentration is more useful than the total protein concentration. Hyperglobulinemia, which has many causes (e.g., heartworms, chronic dermatitis, ehrlichiosis) in a hypoalbuminemic dog can cause the serum total protein concentration to be normal. Severe hypoalbuminemia (i.e., less than 2.0 g/dl) is important diagnostically; it is more commonly found in animals with infiltrative alimentary tract disease, parvoviral diarrhea, intestinal lymphangiectasia, gastrointestinal blood loss, or ascites. It is important to have the serum albumin measured by technology designed for canine and feline albumin; some techniques used for

measuring human albumin result in falsely low measurements of canine albumin.

Ill animals (especially those receiving multiple drugs) are at risk for secondary renal or hepatic failure. Very young and very small animals easily become hypoglycemic if they cannot eat or absorb ingested nutrients. Finally, finding hypercalcemia or hypoalbuminemia may provide a clue to the underlying problem (i.e., make some disorders more likely) in animals with weight loss or anorexia.

### **URINALYSIS**

Urinalysis is required to accurately evaluate renal function and, in conjunction with the urine protein:creatinine ratio, to help identify the cause of hypoalbuminemia. Urine should always be obtained before fluid therapy is begun.

### FECAL PARASITIC EVALUATION

Fecal flotation is indicated in almost every animal with alimentary tract disease or weight loss, especially in puppies and kittens. Even if it is not the primary problem, parasitism may cause additional debilitation. Concentrated salt or sugar solutions are typically used for fecal flotation. The former are usually superior, although incorrectly made solutions may not force heavier ova (e.g., whipworms) to float. Moreover, concentrated salt solutions can distort Giardia cysts, making identification difficult. A zinc sulfate flotation solution is preferred for detecting nematode ova and Giardia cysts. Centrifugation is strongly recommended; it promotes separation of cysts from the fecal matter and results in a more sensitive fecal examination. Some parasites intermittently shed small numbers of ova or cysts, necessitating repeated fecal analyses for diagnosis. Whipworm and Giardia infections can be especially difficult to diagnose.

The ova of the most common tapeworm species are contained in segments and are not found by flotation techniques. Nanophyetus salmincola (the fluke that transmits salmon poisoning) is detected by many flotation solutions, although sedimentation examinations are required to detect most other fluke ova. Cryptosporidiosis can be detected by flotation techniques, but higher magnification (×1000) must be used. The clinician should send the feces to a laboratory that is familiar with this coccidium and is able to perform special procedures to detect it. ELISA methodology is more sensitive than fecal examination for finding cryptosporidia.

Direct fecal examination, although convenient, is not sensitive for nematodes and should not replace flotation techniques. However, occasionally amebiasis, strongyloidiasis, and whipworm infections missed by flotation procedures can be detected in this way. Motile *Giardia* and *Tritrichomonas* trophozoites may be found if the feces are very fresh and the smear is adequately diluted with saline solution. Direct examination seems about half as sensitive as zinc sulfate flotation techniques in detecting giardiasis.

Fecal sedimentation is time-consuming and offers no advantage in detecting common gastrointestinal tract parasites. However, it does detect fluke ova missed by other techniques, especially the ova of Eurytrema spp., Platynosomum spp., and Amphimerus spp. plus Heterobilharzia.

Feces may be preserved by mixing equal volumes of feces and 10% neutral buffered formalin or by using commercially available kits. Polyvinyl alcohol is used in the latter, and feces preserved in this manner can be examined weeks to months later. These techniques are especially useful if one cannot immediately examine feces for protozoal cysts.

### **FECAL DIGESTION TESTS**

Examining feces for undigested food particles by staining thin fecal smears with the Sudan stain (for fat) or iodine (for starch and muscle fibers) is of dubious value. Although the finding of excessive amounts of undigested fecal fat is suggestive of exocrine pancreatic insufficiency (EPI), this test has many false-positive and false-negative results. If EPI is a differential diagnosis, serum trypsin-like immunoreactivity (TLI) is a better way to confirm the diagnosis (see the section on digestion and absorption tests).

Fecal analysis for proteolytic activity (i.e., the fecal trypsin content) also tests for EPI. Qualitative estimates (e.g., fecal film digestion, fecal gelatin digestion) are unreliable. Quantitative analysis is seldom needed because the TLI test is easier and more pleasant to perform. It is rarely necessary to quantitate fecal proteolytic activity to diagnose EPI caused by pancreatic duct obstruction, something TLI does not detect. In this test feces are collected for 3 consecutive days and stored frozen until sent to the laboratory. However, this is an exceedingly rare situation.

Quantitated fecal fat analysis is seldom indicated. Although sensitive for detecting fat malabsorption and maldigestion, it is expensive and unpleasant to perform and does not differentiate malabsorption from EPI.

Fecal occult blood analyses are seldom useful because most pets eat meat by-products that cause a positive reaction. False-positive reactions may also be produced by cimetidine, oral iron preparations, and some vegetables. Furthermore, the sensitivity of different techniques varies, making it difficult to accurately compare results. Finally, blood is often not distributed homogeneously throughout the feces, and a negative result could stem from a sampling error (especially in animals with lower intestinal tract problems).

If analysis for fecal occult blood is desired, the optimal approach is to feed the animal a meat-free diet for 3 to 4 days before performing the test. Tests using the reagents benzidine or orthotoluidine to detect hemoglobin tend to be very sensitive (and hence less specific), whereas those using guaiac are less sensitive (and thus more specific). A sensitive and specific fluorometric method has been validated in dogs. Repeated testing may be necessary to demonstrate intermittent bleeding.

### MISCELLANEOUS FECAL ANALYSES

Enzyme-linked immunosorbent assays (ELISAs) can be used to detect various antibodies or antigens. The test for canine parvovirus seems to be very specific. However, virus may not be found in the feces for the first 24 to 48 hours, and it may be necessary to repeat the test in 2 to 3 days if initial results are negative in a dog strongly suspected of having parvoviral infection. In addition, although dogs with parvoviral diarrhea initially shed large amounts of virus, fecal shedding decreases substantially during the ensuing 7 to 14 days. A repeatedly negative test result therefore does not rule out parvoviral infection, but it does necessitate a consideration of other acute, febrile gastroenteritides (e.g., salmonellosis). This test is particularly valuable if there are epidemiologic considerations (e.g., breeding kennel).

ELISAs for detecting a *Giardia*-specific antigen in human (ProSpecT/Microplate ELISA assay for Giardia, Alexon, Inc.) and canine/feline feecs (SNAP Giardia Test, Idexx Laboratories) are available. The SNAP *Giardia* test appears to be sensitive and specific but has not been carefully compared with multiple zinc sulfate flotation examinations in clinical patients. It has the advantage of being able to be performed in the practice. An IFA test (MERIFLUOR *Cryptosporidium/Giardia* direct immunofluorescent kit, Meridian Bioscience, Inc.) appears to be specific but has the disadvantage of requiring that feecs be sent to a commercial laboratory.

ELISAs for detecting cryptosporidial antigens in feces (ProSpecT Cryptosporidium Microplate Assay, Meridian Diagnostics, Inc. and ProSpecT Cryptosporidium microplate assay, Remel Inc.) appear to be more sensitive than routine fecal examinations. Special staining of fecal smears with a modified Ziehl-Neelsen acid-fast technique is also sensitive, albeit more labor intensive. An IFA test (MERI-FLUOR Cryptosporidium/Giardia direct immunofluorescent kit, Meridian Bioscience, Inc.) was not as sensitive as the ELISAs when looking for cryptosporidia.

Electron microscopy can be used to identify various viral particles (e.g., coronavirus, astrovirus) in feces. Because the ELISA is usually adequate for detecting parvovirus, electron microscopy is rarely necessary. However, it is reasonable to choose this technique if other test results are not diagnostic and there are epidemiologic considerations. Fecal samples for electron microscopy analysis should be obtained early in the disease because fecal viral concentrations may decrease dramatically within 7 to 14 days after the onset of signs. Furthermore, some delicate viruses (e.g., coronavirus) degenerate quickly, and the feces from animals suspected of having such an infection must be handled appropriately if meaningful results are to be obtained. It is important that clinicians contact their laboratory for instructions on sample handling.

Assays for bacterial toxins in feces sometimes help implicate specific bacteria as causing diarrhea. There are numerous ELISA tests available for detecting *Clostridum difficile* toxin in human feces; however, the sensitivity of these tests for canine feces appears to be poor. The tissue culture assay for Clostridum difficile toxin in feces is sensitive but only performed in research laboratories. ELISA tests (Clostridium perfringens Enterotoxin Test, TechLab) and reverse passive latex agglutination tests (Oxoid PET-RPLA, Unipath Co.) tests for Clostridium perfringens enterotoxin are available. However, the results of these tests do not clearly correlate with presence or absence of disease. Their value in clinical cases is still being defined.

There are both culture techniques (InPouch TF, BioMed Dianonstics) and polymerase chan reaction (PCR) tests for *Tritrichomonas fetus* in feline feces. The culture technique can be done in the practice and appears to be sensitive and specific; it is more sensitive than direct fecal examination.

# BACTERIAL FECAL CULTURE

Fecal culture is seldom indicated in small animals unless a contagious disease is strongly suspected or other test findings (e.g., endoscopy and biopsy) are nondiagnostic. Specific culture techniques for the detection of each pathogen are recommended. Therefore the clinician should contact the laboratory before submitting feces, informing them specifically what bacteria to attempt to grow and following their instructions regarding the handling of specimens. It is important to remember that fecal culture cannot be used to diagnose small intestinal antibiotic-responsive enteropathy (ARE).

The pathogens most likely to be cultured from feces from small animals are C. perfringens, C. difficile, Salmonella spp., Campylobacter jejuni, Yersinia enterocolitica, and verotoxinproducing strains of Escherichia coli. Confirmation of toxin production of isolates can be performed using PCR techniques or bioassay. Aeromonas spp. and Plesiomonas spp. may also cause diarrhea. Salmonella spp. are best cultured by inoculating at least 1 g of fresh feces into an enrichment medium and subsequently a selective medium specific for Salmonella spp. It is sometimes possible to culture Salmonella from the colonic mucosa. A PCR technique has been used recently in the evaluation of equine feces and may be useful for the evaluation of canine and feline feces. To culture C. jejuni, very fresh feces must be inoculated onto selective media and incubated at approximately 40° C instead of 37° C. If inoculation is to be delayed, special transport media should be used, not routine commercial transport devices (e.g., culturette swabs). PCR testing is available for Campylobacter spp. in canine and feline feces (GI Lab, Texas A&M University). The clinical value is still being defined.

It is important to note that the mere presence of any of these bacteria in an animal's feces does not confirm that they are causing disease. Culture results must be correlated with clinical signs and the results of other laboratory tests.

Candida spp. are occasionally cultured from feces. The finding is often of uncertain significance, but the organisms may cause problems in some animals (e.g., those receiving chemotherapy).

### CYTOLOGIC EVALUATION OF FECES

Fecal cytologic evaluations may identify etiologic agents or inflammatory cells. In this method a thin, air-dried smear is stained with Gram's or a Romanowsky-type stain (e.g., Diff-Quik). The latter identifies cells better than Gram's stain does.

Finding excessive numbers of spore-forming bacteria (e.g., more than 3 to 4 per 1000× field) was once thought to strongly suggest clostridial colitis (see Fig. 33-1). However, the presence of spores is neither specific nor sensitive for clostridial colitis. Finding that the bacterial population is relatively uniform morphologically is of uncertain value, other than to show that the normal bacterial flora is disrupted. However, no comments can be made relative to cause or effect.

Short, curved, gram-negative rods (i.e., "commas" or "seagull wings") are suggestive of campylobacteriosis. The larger spirochetes, which are often plentiful in diarrheic feces, are not *C. jejuni* and are of uncertain pathogenicity. Although cytologic preparations are not critically analyzed in diarrheic small animals, fecal cytologic analysis for *Campylobacter* spp. is a specific, albeit insensitive, method in people. Fungal organisms (e.g., *Histoplasma capsulatum*, *Cyniclomyces guttulatus Candida* spp.) are rarely found by fecal examination; cytologic examination of mucosal scrapings or histologic examination of biopsy specimens is usually necessary to diagnose histoplasmosis.

The finding of leukocytes in feces indicates the presence of a transmural colonic inflammation instead of just a superficial mucosal inflammation. However, a definitive diagnosis of a particular cause is not possible.

# RADIOGRAPHY OF THE ALIMENTARY TRACT

Imaging (i.e., radiography) allows structures to be evaluated that cannot be adequately assessed during physical examination (e.g., esophagus, stomach) and may detect abnormalities missed by abdominal palpation (e.g., gastric mass, foreign object, splenic parenchymal mass). Plain radiographs should always be obtained before contrast-enhanced radiographs because (1) the former may yield diagnostic findings, (2) contrast-enhanced radiographs may be contraindicated, and (3) plain radiographs are needed to ensure a correct radiographic technique during the contrast procedure. Contrast-enhanced radiographs may be able to detect abnormalities (e.g., a gastric outflow tract obstruction) that plain radiographs cannot.

Radiographs are generally useful in the diagnostic workup of animals with dysphagia, regurgitation, vomiting, abdominal mass or distention, abdominal pain, or acute abdomen. They are occasionally helpful in animals with constipation, weight loss, or anorexia of unknown cause, but other tests are usually indicated first in such animals and often render imaging unnecessary. Radiographic findings are rarely diag-

nostic in dogs or cats with diarrhea or copious abdominal effusion.

# ULTRASONOGRAPHY OF THE ALIMENTARY TRACT

Ultrasonography may be done in combination with or instead of radiography; however, it is extremely operator dependent. It is often useful in animals with an acute abdomen, abdominal effusion, vomiting, diarrhea, weight loss, or anorexia of unknown cause and also in those with an abdominal mass, distention, or pain. Ultrasonography can be used to identify pancreatitis, infiltrations in various organs, and intussusceptions that radiography misses. Furthermore, effusions, which render radiographs useless, enhance ultrasonographic contrast. Ultrasonography can be more informative than radiography when determining whether an animal with an acute abdomen requires surgery. Finally, ultrasonography can be used to guide the percutaneous aspiration and biopsy of intraabdominal lesions that would otherwise necessitate surgery or laparoscopy.

### **Techniques**

A 5 MHz probe is probably the most utilitarian. Hair is often clipped so that there is no trapped air that could compromise the quality of the image. Fluid can be infused into the abdomen or stomach to improve the evaluation, but this is infrequently needed.

# Findings

The thickness, echodensity, and homogeneity of organs (e.g., liver, spleen, intestine, stomach, mesenteric lymph nodes, masses) may be assessed. Intraparenchymal infiltrates that cannot be detected radiographically may also be found. The particular ultrasonographic findings seen in specific disorders of the alimentary tract are discussed in subsequent chapters dealing with the disorders.

# IMAGING OF THE ORAL CAVITY, PHARYNX, AND ESOPHAGUS

### **INDICATIONS**

Animals with dysphagia, oral pain, halitosis of unknown cause, or a swelling or mass should generallly undergo imaging. If dysphagia of neuromuscular origin is suspected, dynamic studies (i.e., fluoroscopy) are recommended. Ultrasonography can be particularly informative in the evaluation of any infiltrates or masses.

### **Techniques**

Anesthesia is necessary so that animals can be properly positioned for radiographs of the skull. Lateral, dorsoventral (DV), and oblique views are used to detect foreign objects or fractures. Open-mouth ventrodorsal (VD) views and end-on views of the nose may also be helpful. However,

dynamic studies (i.e., fluoroscopy, cinefluoroscopy) are necessary if one is looking for dysphagia of neuromuscular origin. These studies are performed by feeding conscious animals various forms of barium (i.e., liquid, paste, and mixed with food).

### **Findings**

Foreign objects, fractures, bone lysis, soft tissue masses or densities, and emphysema are commonly found. The bone surrounding the tooth roots should be examined for evidence of lysis and the temporomandibular joints for signs of arthritis. It is important to remember to consider the bilateral symmetry of the skull; one side should be compared with the other when evaluating the VID projection. When performing contrast-enhanced or dynamic studies, the clinician should watch for the aspiration of barium, the strength with which the bolus is propelled into the esophagus, and the synchronization of the opening of the cricopharyngeal muscle with the pharyngeal phase of swallowing.

# INDICATIONS FOR IMAGING OF THE ESOPHAGUS

Indications for evaluating the esophagus include regurgitation (including pharyngeal dysphagia), pain when swallowing, unexplained recurrent pneumonia or cough, and thoracic "masses" (seen radiographically) of undetermined origin. A barium contrast—enhanced esophagram is necessary unless plain films reveal the presence of an esophageal foreign object, evidence of esophageal perforation (e.g., a pleural effusion or pneumothorax), or an obvious hiatal hernia. Finding obvious megaesophagus on plain radiographs is usually considered sufficient, but some dogs with megaesophagus on plain radiographs demonstrate normal function when barium is administered. Ultrasonography is seldom useful for dogs and cats with esophageal disease, unless there is a thoracic mass.

### **Techniques**

Liquid barium is the best contrast agent for esophageal studies; it provides excellent detail and, if aspirated, is not as noxious as paste or food. The clinician must be careful not to administer drugs that affect esophageal motility (e.g., xylazine, ketamine, anesthesia). The animal should take several swallows of dilute barium from a syringe, after which right lateral and VD views are quickly obtained. If possible, the clinician should perform fluoroscopy as the animal swallows the barium to assess esophageal motility and look for partial esophageal obstruction, segmental esophageal weakness, gastroesophageal reflux, and esophageal-pharyngeal reflux (i.e., cricopharyngeal incompetence). Radiographs may be taken if a lesion is found fluoroscopically. If fluoroscopy is not available, multiple radiographs (usually lateral projections) are taken in rapid succession, beginning very shortly (i.e., 5 to 10 seconds) after swallowing.

Barium paste is acceptable if liquid is not available. Hypertonic, iodine-contrast agents do not achieve as good a contrast as barium and cause severe problems if aspirated; isotonic water-soluble iodine contrast agents are better. If radiographic studies performed with liquid or paste contrast agents do not detect an abnormality in an animal in which esophageal disease is strongly suspected, the study should be repeated using a mixture of barium and food (both canned food and dry kibble). Such studies may detect partial strictures or muscular weakness not found in previous studies.

If barium is retained in the esophagus but little or none enters the stomach, the animal should be held in a vertical position so that gravity facilitates the migration of barium into the stomach. If barium readily enters the stomach, this indicates that there is no lower esophageal sphincter obstruction. If a hiatal hernia is suspected but not seen, a lateral radiograph of the caudal thorax may be taken while the abdomen is manually compressed. This is done in an attempt to force the stomach to herniate into the thorax so that the hernia can be demonstrated.

If esophageal disease seems likely but is not found by static radiographs, fluoroscopic studies are required. It may be necessary to observe the esophagus for several minutes (or longer) before some abnormalities (e.g., gastroesophageal or esophageal-pharyngeal reflux) occur. In animals with marginal esophageal disease, fluoroscopy may be necessary to document that primary or secondary esophageal waves are present but are either weak or not readily stimulated.

If an esophageal perforation is suspected (e.g., septic pleuritis or mediastinitis, pneumomediastinum or pneumothorax), an isotonic, iodine contrast medium may be used. However, the only purpose of such a study is to localize the perforation. If the clinician already knows where the leakage is likely to be (e.g., there is a bone foreign body in the esophagus), radiographs are of dubious value; exploratory surgery is usually a better option.

### **Findings**

Esophageal dilation, foreign objects, soft tissue densities, spondylosis suggestive of spirocercosis, and hiatal hernia may often be identified on plain films. An air-filled esophagus is not always diagnostic of pathologic esophageal weakness. Although it is tempting to use plain radiograph findings as the basis for the diagnosis of esophageal disease when there is an "obvious" abnormality, it is easy to misinterpret plain films or miss abnormalities that a barium contrastlenhanced study reveals. Even the finding of a dilated, gasfilled esophagus on plain thoracic films does not definitively diagnose "megaesophagus." Rarely, animals with a dilated, air-filled esophagus on plain films are found to have normal esophageal function when evaluated with barium contrastenhanced radiographs (Fig. 29-1). Likewise, the appearance of an accumulation of foodlike material in the classic location for a vascular ring anomaly may be caused by a localized esophageal weakness or a thymic cyst.

Many foreign objects in the esophagus (e.g., bones) can be seen on plain radiographs. However, excellent radiographic technique is necessary because some bones (especially poultry bones) as well as rawhide treats are relatively radiolucent (Fig. 29-2). An esophageal perforation some-

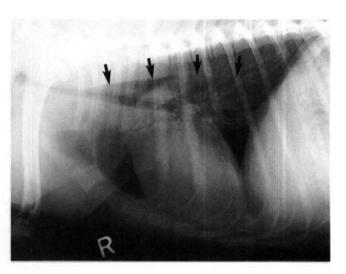


FIG 29-1
Lateral thoracic radiograph from a dog that was seen because of coughing. Note the dilated, air-filled esophagus (arrows). Contrast-enhanced esophagram (with fluoroscopy) obtained 2 days later documented normal esophageal size and function.

times causes pneumothorax, emphysematous mediastinitis, or a pleural or mediastinal effusion.

Contrast-enhanced esophagrams should be considered in animals with suspected esophageal disease and in those with unidentified thoracic masses because many esophageal tumors radiographically resemble pulmonary parenchymal masses (see Fig. 31-5). Contrast-enhanced esophagrams may also show that structures that seemingly involve the esophagus actually do not. An obstruction is suggested on contrast-enhanced esophagrams if the barium column terminates abruptly as it travels caudally; weakness usually causes contrast to be retained throughout the esophagus (Fig. 29-3) unless it is segmental. A partial obstruction is suggested by the retention of barium-impregnated food but not of liquid or paste (see Fig. 31-4).

A barium contrast study may reveal malpositioning (e.g., hiatal hernia; see Fig. 31-2). However, the finding of a properly positioned structure on one study does not ensure that it will stay properly positioned (e.g., some hiatal hernias slide in and out of the diaphragm and may be normally positioned when the radiograph is taken). Gastroesophageal reflux and esophagitis also may be difficult to diagnose radiographically. Barium may adhere to a severely diseased mucosa, but less severe esophagitis may not be detected. In addition, normal dogs may have an episode of gastroesophageal reflux during a contrast study, whereas dogs with pathologic gastroesophageal reflux may not have reflux during a short examination.

If the animal is believed to be regurgitating but the barium contrast—enhanced radiographs are unrevealing, either the assessment of regurgitation is wrong or there is occult disease, in which case reexamination of the esophagus with fluoroscopy or endoscopy or both must be done.



FIG 29-2

**A,** Lateral thoracic radiograph from a dog with a foreign object in the esophagus (arrows). Note the concomitant pleural effusion. A chicken bone had perforated the esophagus, and septic pleuritis was present. (**A** from Allen D, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.) **B,** Lateral thoracic radiograph from a dog with a rawhide treat in the esophagus. The density representing the bone (arrows) is more diffuse than was seen in **A** and looks more like a pulmonary parenchymal density than a bone.

# IMAGING OF THE STOMACH AND SMALL INTESTINE

# INDICATIONS FOR RADIOGRAPHIC IMAGING OF THE ABDOMEN WITHOUT CONTRAST MEDIA

Indications for plain abdominal radiography may include vomiting, acute abdomen, constipation, abdominal pain, enlargement, distention, or a mass. Plain radiographs are rarely beneficial in animals with a marked abdominal effusion (the fluid obliterates serosal detail) or with chronic diarrhea. Plain radiography is often not as cost-effective when the abdomen can be palpated thoroughly as when the area is difficult to examine (e.g., large or obese animals or animals in pain). In vomiting animals plain abdominal radiographs can be especially helpful in detecting radiodense

foreign objects and alimentary tract dilation resulting from obstruction, foreign objects, or masses.

### **Techniques**

The clinician always should obtain two radiographic views, usually right lateral and VD projections. Cleansing enemas may improve the diagnostic usefulness of radiographs in patients with a great deal of feces; however, a critically ill animal or one with an acute abdomen generally should not have an enema unless plain radiographs show it is necessary.

### **Findings**

Plain abdominal radiographs may detect masses, foreign objects, a gas- or fluid-distended hollow viscus, misshapen or emphysematous parenchymal organs, pneumoperito-

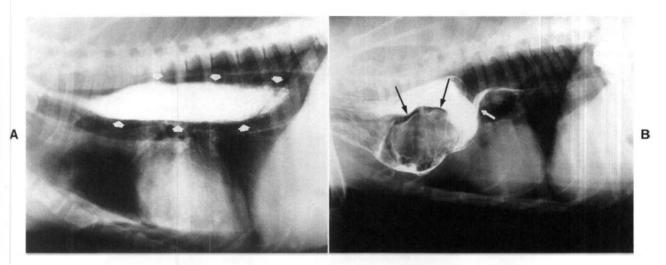


FIG 29-3

**A,** Lateral thoracic contrast-enhanced esophagram from a dog with generalized esophageal weakness. Note that barium is retained throughout the length of the esophagus (arrows). **B,** Lateral thoracic contrast-enhanced radiograph of a dog with an esophageal obstruction caused by a vascular ring anomaly. The column of barium stops abruptly (short arrow) in front of the heart, a finding characteristic of a persistent fourth aortic arch. A filling defect is also displacing barium in the dilated portion of the esophagus (long arrows). (Courtesy Dr. Phillip F. Steyn, Colorado State University, Fort Collins, Colo.)

neum, abdominal effusions, and displaced organs suggestive of a mass or adhesion.

Gastric outflow tract obstruction is easy to diagnose when there is marked gastric distention (Fig. 29-4). However, if the patient has recently vomited, the stomach may be empty and contracted. Gastric dilation, especially with volvulus, is easily recognized (see Fig. 32-4). Radiodense foreign objects are easily seen, but radiolucent foreign objects are seen only if they are outlined by swallowed air.

Intestinal obstructions are usually easier to diagnose on the basis of plain radiograph findings than are gastric obstructions; obstructed intestines distended with air, fluid, or ingesta are not readily emptied when the patient vomits (unless it is a high, duodenal obstruction). However, intestinal distention (i.e., ileus) may be caused by inflammation (i.e., adynamic or physiologic ileus) as well as obstruction (i.e., mechanical, occlusive, or anatomic ileus). Anatomic ileus (i.e., obstruction) typically produces a nonuniform intestinal distention with a greater degree of distention than is seen with physiologic ileus (Fig. 29-5). If "stacking" of the distended intestines or sharp bends and turns in the dilated intestines are seen, this also suggests anatomic ileus. Lateral radiographs obtained with the animal standing rarely aid in differentiating anatomic from physiologic ileus. Even experienced radiologists occasionally misdiagnose physiologic ileus as representing an obstruction. Thus diseases producing severe inflammation (e.g., parvoviral enteritis) may clinically and radiographically mimic an intestinal obstruction.

Special types of intestinal obstruction are associated with unique radiographic findings. If the entire intestinal tract is uniformly distended with gas (Fig. 29-6) and the clinical signs fit, mesenteric volvulus may be diagnosed. If marked

intestinal distention is found but is very localized and seems out of place (e.g., has herniated), a strangulated or incarcerated intestinal obstruction (see Fig. 33-9) should be considered.

Linear foreign bodies rarely produce gas-distended bowel loops. Instead, they tend to cause the intestines to bunch together, and sometimes small gas bubbles are present (see Fig. 33-10). This occurs because the intestines "gather" around the linear foreign object as they try to propel it aborad. This "gathering" or "bunching" plus the fact that linear foreign bodies tend primarily to affect the upper small intestines (i.e., duodenum) mean that it is rare that they cause gas-distended loops of bowel. Sometimes pleated (i.e., "accordian-like") intestines can be seen on plain radiographs (see Fig. 33-10).

It is difficult to determine the thickness of intestines on plain radiographs. Animals with diarrhea and an increased amount of intestinal fluid are often misdiagnosed as having thickened intestinal walls.

Decreased serosal contrast is due to either lack of fat or excessive abdominal fluid (see Chapter 36). Displacement of an organ (Fig. 29-7) often means that there is a mass present. Pneumoperitoneum is diagnosed if both the thoracic and abdominal surfaces of the diaphragm or the serosal surfaces of the liver, stomach, or kidneys are easily seen (see Fig. 34-1, *A*). Pneumoperitoneum may also be documented by the finding of only a few gas bubbles in the peritoneal cavity (see Fig. 34-1, *B*).

# INDICATIONS FOR ULTRASONOGRAPHY OF THE STOMACH AND SMALL INTESTINES

Ultrasonography usually reveals almost any soft tissue change that plain radiographs detect in addition to infiltrations that

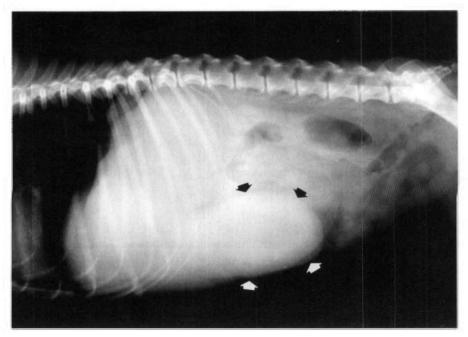


FIG 29-4
Plain lateral radiograph from a dog with gastric outflow obstruction. Note the dilated stomach protruding past the costal arch (arrows).

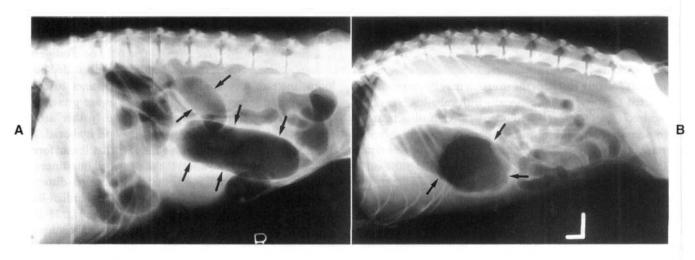


FIG 29-5

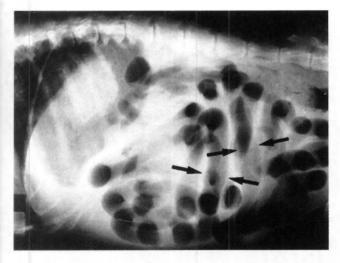
**A,** Plain lateral abdominal radiograph from a dog with an intestinal obstruction causing intestinal distention. Note the markedly increased diameter of the small intestinal lumen (arrows). **B,** Plain lateral abdominal radiograph from a dog with peritonitis causing physiologic ileus. Note the lesser degree of small intestinal distention compared with that in **A.** The large gas-filled structure is the gastric pylorus (arrows). (Courtesy Dr. Kenita Rogers, Texas A&M University, College Station, Tex.)

radiographs cannot detect. Ultrasonography is particularly useful for detecting intussusceptions, pancreatitis, abdominal infiltrative disease, and small amounts of effusion not seen radiographically; for evaluating the hepatic parenchyma; and for identifying abdominal neoplasia in animals with a substantial effusion. Ultrasonography is much more revealing than radiography in animals with minimal body fat that have little or no radiographic contrast in the abdomen. However, very dehydrated animals may be difficult to image,

and it is easy to miss small foreign objects (especially in the stomach if there is food and gas present). Ultrasonography will not detect bony changes and modest microhepatica that are easily detected by radiographs. The skill of the ultrasonographer determines the usefulness of the technique.

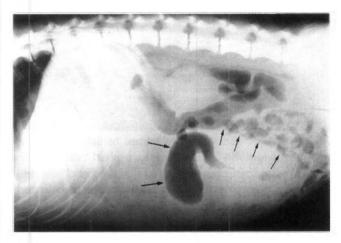
### **Technique**

Before ultrasonography is performed, the abdominal hair usually should be clipped to improve the quality of the



#### FIG 29-6

Lateral abdominal radiograph from a dog that had an acute onset of vomiting, abdominal pain, and shock. There is a uniform intestinal distention that is not as great as that in Fig. 29-5, A. However, distention is more than that seen in Fig. 29-5, B. Some intestinal loops have assumed a vertical orientation (arrows), which suggests the existence of an obstruction. This dog had a mesenteric volvulus. (Courtesy Dr. Susan Yanoff, U.S. Military.)



#### FIG 29-7

Lateral abdominal radiograph from a dog with a large granuloma caused by pythiosis. Small intestinal loops are displaced dorsally and caudally (small arrows). The border of the mass is not discernible except where it displaces small intestinal loops. The finding of a dilated intestinal loop (long arrows) is consistent with obstruction.

examination. This is not necessary in animals with minimal hair. Because air in the stomach or intestines limits the usefulness of ultrasonography, exercise, drugs (e.g., some narcotics) that cause hyperventilation, and enemas should be avoided before the examination.

# **Findings**

Ultrasonography should detect almost any soft tissue change that plain radiographs detect, plus gastric and intestinal infiltrates (Fig. 29-8, A), intussusceptions (Fig. 29-8, B), enlarged lymph nodes (Fig. 29-8, C), masses (Fig. 29-8, D), some radiolucent foreign objects, and small amounts of free peritoneal fluid that radiographs cannot detect. If tissue infiltrates are found, they can sometimes be aspirated by the fine-needle technique.

## INDICATIONS FOR CONTRAST-ENHANCED GASTROGRAMS

Contrast-enhanced gastrography is principally performed in vomiting animals when ultrasound studies and plain abdominal radiographs are unrevealing. It is primarily used to detect a gastric outflow tract obstruction, gastric masses/foreign bodies, and gastric motility problems.

# **Technique**

The animal should not be allowed to eat for at least 12 hours (preferably 24 hours) before the procedure, and feces should be removed with enemas. Plain radiographs should be obtained immediately before the contrast-enhanced films to verify that the abdomen has been properly prepared and the radiographic technique is correct and to determine whether the diagnosis cannot be made on the basis of the plain radiographic findings. Liquid barium sulfate is then administered orally (8 to 10 ml/kg in small dogs and cats and 5 to 8 ml/kg in large dogs). Iohexol can be administered orally (i.e., 700 to 875 mg I/kg, which is about 11/4 to 11/2 ml/kg). The agent should be administered via a stomach tube to ensure adequate gastric filling and optimal evaluation of the stomach. The animal should not receive motility-altering drugs (e.g., xylazine, parasympatholytics), which delay outflow.

Immediately after barium administration, radiographs are taken in the left and right lateral plus DV and VD projections. Radiographs in the lateral and DV projections should be obtained again at 15 and 30 minutes and perhaps also at 1 to 3 hours. The right lateral view causes barium to pool in the pylorus, the left lateral view causes it to pool in the gastric body, the DV view causes it to pool along the greater curvature, and the VD view allows better evaluation of the pylorus and antrum. Double-contrast gastrograms provide more detail than single-contrast gastrograms. They are performed by administering barium via a stomach tube, then removing most of the barium through the same tube and insufflating the stomach with gas until it is mildly distended.

If available, fluoroscopy is best performed immediately after administration of the barium. It can be used to evaluate gastric motility, gastric outflow, and the maximal opening size of the pylorus. If the animal is fed barium mixed with food (only recommended if gastric outflow tract obstruction is suspected despite normal liquid barium study findings), gastric emptying will be markedly delayed compared with that seen when the animal is fed liquid barium.

### **Findings**

Gastric emptying is considered delayed if liquid barium does not enter the duodenum 15 to 30 minutes after administration or if the stomach fails to almost completely empty a

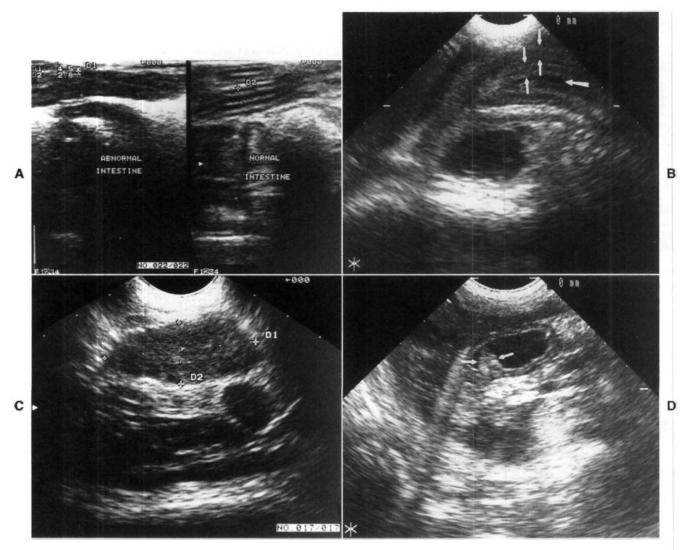


FIG 29-8

**A,** Ultrasonographic image of two sections of small intestine from a cat with an alimentary tract lymphoma. The normal intestine on the right is 2.8 mm thick (see the two "+'s" noted as D2), whereas the abnormal intestine on the left is 4.5 mm thick (D1) because of neoplastic infiltrates. **B,** Ultrasonographic image of an ileocolic intussusception that was not obvious on plain abdominal radiographs. There are two intestinal walls (small arrows) seen on each side of the lumen (large arrow). **C,** An enlarged mesenteric lymph node in a dog caused by lymphoma, seen by ultrasonography. The lymph node was not detected on radiographs or by abdominal palpation. **D,** Ultrasound image of the gastric antrum from a dog with benign gastric polyps. One polyp can be seen (arrows) protruding into the gastric lumen. (Courtesy Dr. Linda Homco, Cornell University, Ithaca, N.Y.)

liquid barium meal in 3 hours (see Fig. 32-2). Luminal filling defects (e.g., growths and radiolucent foreign objects), ulcers, pyloric lesions preventing gastric emptying, and infiltrative lesions may be seen using this method (see Fig. 32-2, *C*). However, normal peristalsis, ingesta, or gas bubbles may resemble an abnormality; therefore a change must be seen on *at least* two separate films before the clinician can diagnose disease.

Contrast-enhanced gastrograms are not as sensitive as endoscopy for detecting gastric ulceration, and they cannot detect erosions. Ulcers are documented radiographically if barium is seen to enter the gastric or duodenal wall or if a persistent spot of barium is identified in the stomach long after the organ has emptied itself of the contrast agent (see Fig. 32-6). The duodenum should be scrutinized in a search for constrictions and infiltrative lesions because many vomiting animals have disease there (e.g., inflammatory bowel disease, tumors) rather than in the stomach (see Chapter 33).

# INDICATIONS FOR CONTRAST-ENHANCED STUDIES OF THE SMALL INTESTINE

Vomiting is the principal reason for performing contrast studies of the upper small intestine. Contrast-enhanced radiographs are particularly useful for distinguishing anatomic from physiologic ileus. Orad obstructions are easier to demonstrate than aborad ones if the contrast medium is administered orally. If a very aborad obstruction is suspected (e.g., ileocolic intussusception), a barium enema (or preferably ultrasonography) is often better than an upper gastrointestinal contrast series. Although linear foreign objects usually produce subtle findings on plain radiographs, they often cause a classic "pleating" or "bunching" of the intestines to be seen on contrast films (see Fig. 33-10, *C*).

Animals with diarrhea seldom benefit from contrast studies of the intestines because normal radiographic findings do not exclude the presence of severe intestinal disease, and even if radiographic findings indicate the presence of infiltrative disease, it is still necessary to obtain a biopsy specimen to determine the cause. Contrast series are sometimes useful if the clinician is trying to decide whether to perform endoscopy or surgery. However, it is usually more cost-effective to perform endoscopy or surgery and skip the contrast-enhanced radiographs.

Use of iodinated contrast agents (preferably iohexol) is reasonable if an alimentary tract perforation is suspected. However, if spontaneous septic peritonitis is strongly suspected, it can usually be definitively diagnosed by ultrasound-guided abdominocentesis and fluid analysis. If ultrasound is unavailable and blind abdominocentesis is unrevealing in such a patient, it is usually better to perform a thorough exploratory laparotomy than contrast-enhanced radiography.

# **Technique**

Liquid barium sulfate is administered as described for contrast-enhanced gastrography. Lateral and VD radiographs should be obtained immediately and then 30, 60, and 120 minutes after barium administration. Additional films are obtained as necessary. The study is completed once contrast has reached the colon. If chemical restraint is absolutely necessary, acetylpromazine may be used. Fluoroscopy is rarely needed for these studies.

Hypertonic iodinated contrast agents are inferior to barium for small intestinal studies because they decrease the intestinal transit time and can cause considerable fluid shifts by osmotically drawing fluid into the gastrointestinal tract. Their potential advantages rarely outweigh the disadvantages. Iohexol is safer and produces better detail than the hypertonic iodinated compounds.

### Findings

In a complete intestinal obstruction, the barium column cannot advance beyond a certain point, and the intestines orad to this point are typically dilated. A partial obstruction may be denoted by delayed passage past a certain point (there may or may not be dilation of the intestines orad to this point) or constriction of the lumen. Because it is easy to overinterpret contrast-enhanced radiographs of the intestines, changes must be seen on *at least* two different films taken at different times before a disease is diagnosed.

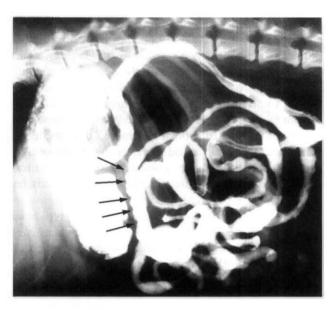


FIG 29-9
Lateral contrast-enhanced radiograph from a dog with duodenal lymphoma. Note the scalloped appearance to the margin of the small intestine (arrows).

"Enteritis" is often incorrectly diagnosed if a fine "brush border" in the lumen is found. However, this finding actually results from the barium normally distributing itself among villi, not from enteritis. Infiltration is denoted by scalloped margins (sometimes called *thumb-printing*); such a pattern (Fig. 29-9) may be seen in the setting of neoplasia (e.g., lymphoma), inflammatory bowel disease, fungal infection (e.g., histoplasmosis), or parvoviral enteritis. However, its absence does not rule out the presence of infiltrative disease. Focal dilations not caused by obstruction (i.e., diverticula) are rare and usually represent a localized neoplastic infiltrate. In rare instances, unsuspected intestinal blind loops or short-bowel syndromes may be detected. Motility problems may cause slowed passage of the contrast through the alimentary tract.

# INDICATIONS FOR BARIUM CONTRAST ENEMAS

If ultrasound and flexible colonoscopy are available, there is seldom any need for barium enemas. If only rigid colonoscopy is available, barium enemas are needed to evaluate the ascending and transverse colon, areas inaccessible to rigid scopes. If colonoscopy is unavailable, a barium enema may be useful for looking for infiltrative lesions (e.g., rectal-colonic neoplasia causing hematochezia), a partial or complete obstruction, or ileocolic or cecocolic intussusception. It can also evaluate the colon orad to a near-complete rectal obstruction to determine whether there are more infiltrative lesions or obstructions besides the one palpated near the rectum.

### **Technique**

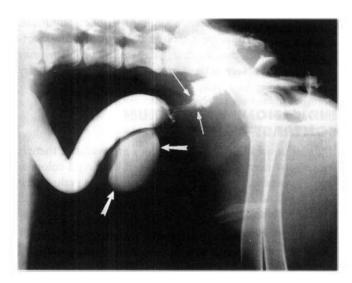
The patient should be fasted for at least 24 hours, and then the colon must be emptied and cleaned by enemas or alimentary tract lavage solutions, or both. The animal should be anesthetized and a balloon-tipped catheter placed in the colon. The balloon is then inflated so that barium cannot leak out the rectum. Approximately 7 to 10 ml of liquid barium/kg at body temperature is infused into the colon until it is uniformly distended, and lateral and VD radiographs are obtained. The colon may then be emptied of barium and insufflated with air to achieve a double-contrast barium enema, which provides greater detail. If too much barium is administered, the ileum may fill with the contrast agent, obscuring colonic detail and making the study less useful.

### **Findings**

Barium enemas unreliably detect mucosal disease (i.e., ulcers, inflammation). If the animal has been properly prepared, these enemas can reveal intraluminal filling defects representing ileocolic or cecocolic intussusception (see Fig. 33-11), proliferative colonic neoplasia (e.g., polyps, adenocarcinoma), extraluminal compression denoted by smooth-surfaced displacement of the barium from the colonic lumen, and infiltrative disease (i.e., a roughened, partial obstruction or an "apple core" lesion) (Fig. 29-10). However, it is imperative that a change be found on *at least* two films to ensure that it is not an artifact.

### PERITONEAL FLUID ANALYSIS

Fluid analysis is discussed in detail in Chapter 36. The fluid is obtained by performing abdominocentesis with a syringe and needle. If this technique fails, a multifenestrated



### FIG 29-10

Lateral view of a dog that had a barium enema. There is circumferential narrowing with roughened borders (thin arrows) that is in distinction to the rest of the colon. This dog had infiltrative adenocarcinoma, which caused an obstruction. The urinary bladder is also seen as a result of the previous contrast procedure (thick arrows).

catheter (e.g., a dialysis catheter, a sterile teat cannula, or an 18-gauge cephalic catheter with additional holes cut with a scalpel) may be successful. It is sometimes best to allow fluid to drain out of the catheter without applying negative pressure.

If peritoneal inflammation is suspected but abdominal fluid cannot be retrieved, a diagnostic peritoneal lavage may be performed. In this method a sterile catheter (preferably with multiple fenestrations) is inserted into the abdomen and warm, sterile physiologic saline solution (20 ml/kg) is administered rapidly. The abdomen is massaged vigorously for 1 to 2 minutes, and then some of the fluid is aspirated. The aspirate is evaluated cytologically.

# **DIGESTION AND ABSORPTION TESTS**

Exocrine pancreatic function may be tested by measuring fecal proteolytic activity (not recommended), fat absorption with and without pancreatic enzymes (not recommended), or serum TLI (recommended).

Fat absorption testing is simple but of questionable sensitivity and specificity. It is no longer recommended. The reader is referred to prior editions of this text for a description of the test and interpretation.

Serum TLI is the most sensitive and specific test for EPI and is convenient (i.e., submit 1 ml of refrigerated serum obtained after an overnight fast) and readily available. The TLI assay detects circulating proteins produced by a normally functioning exocrine pancreas and is even valid in animals receiving pancreatic enzyme supplements orally. Pancreatitis, renal failure, and severe malnutrition may increase the serum TLI concentrations, but this rarely causes results to be misinterpreted. However, if EPI is caused by obstruction of the pancreatic ducts (apparently rare) as opposed to acinar cell atrophy or destruction (common), the serum TLI test may not detect maldigestion. In such cases, a quantitative fecal proteolytic assay is required.

Normal dogs have serum TLI activities of 5.2 to 35  $\mu$  g/L. Values of less than 2.5  $\mu$ g/L confirm a diagnosis of EPI. Normal cats have higher values (28 to 115  $\mu$ g/L). The serum TLI assay is primarily indicated in dogs with chronic small intestinal diarrhea or chronic weight loss of unknown origin. Because feline EPI is rare, the test is seldom necessary in cats. Although principally used to detect EPI, serum TLI values substantially greater than normal are suggestive of pancreatitis.

# SERUM CONCENTRATIONS OF VITAMINS

Serum concentrations of cobalamin and folate are sometimes helpful in animals with chronic small intestinal diarrhea or chronic weight loss. These tests may provide evidence of severe small intestinal mucosal disease. Dietary cobalamin is absorbed in the intestine, principally the ileum. When ARE is present, bacteria sometimes bind cobalamin and prevent

its absorption, decreasing the serum concentrations. Cobalamin concentrations are usually decreased in dogs with EPI, possibly because of the high incidence of ARE in such animals. Severe mucosal disease, especially in the region of the ileum, may also cause serum cobalamin concentrations to be decreased, ostensibly because of malabsorption of the vitamin. Perhaps the major indications for measuring serum cobalamin are to look for evidence of intestinal disease in patients with weight loss of uncertain cause and to better define cats with known small intestinal disease (cobalamin-deficient cats can experience metabolic complications). If the serum cobalamin is low in a patient with weight loss of unknown cause, it is likely that small intestinal disease is responsible. B-complex vitamin supplementation may cause an increased serum cobalamin concentration.

Dietary folate is absorbed in the small intestine. If there are many bacteria in the upper small intestine, these sometimes synthesize and release folate, causing the serum concentrations to be increased. Likewise, severe intestinal mucosal disease may decrease absorption, causing lower serum concentrations. B-complex vitamin supplementation may increase serum folate concentrations.

Because bright light degrades cobalamin, samples should be frozen and kept in the dark during storage and transport. The specificity of decreased serum cobalamin and increased folate concentrations for ARE is questionable.

# OTHER SPECIAL TESTS FOR ALIMENTARY TRACT DISEASE

Antibodies to acetylcholine receptors should be measured if the clinician is looking for a cause of dysphagia or esophageal weakness that could be of neuromuscular origin (see p. 422). Serum is obtained and sent to a laboratory that can perform a validated assay for the species being evaluated. Increased titers to such antibodies are strongly suggestive of myasthenia gravis, even if there are no systemic signs. False-positive results are rare. Testing can be done by Dr. Diane Shelton (Comparative Neuromuscular Laboratory, Basic Science Building, University of California at San Diego, La Jolla, CA 92093-0612).

Measurement of antibodies to 2M muscle fibers can be helpful in dogs with suspected masticatory muscle myositis (see p. 420). These antibodies are typically not found in dogs with polymyositis, whereas most dogs with masticatory myositis have them. Serum is required for the test and can be sent to Dr. Diane Shelton for testing.

Serum gastrin concentrations are measured in animals with signs suggestive of gastrinoma (i.e., chronic vomiting, weight loss, and diarrhea in older animals, especially if there is concurrent esophagitis or duodenal ulceration). Gastrin stimulates gastric acid secretion and is trophic for the gastric mucosa. Serum for assay of gastrin is harvested from an animal after an overnight fast and rapidly frozen. The serum gastrin concentration may be increased in animals with gastrinoma, a gastric outflow tract obstruction, renal failure,

short-bowel syndrome, or atrophic gastritis and in those receiving antacid therapy (e.g.,  $H_2$ -receptor antagonist and proton pump inhibitors). Resting serum gastrin concentrations may vary, with occasional values in the normal range in animals with gastrinoma. Provocative testing should be considered in dogs strongly suspected of having gastrinoma but with normal baseline serum gastrin concentrations (see Chapter 52).

Testing for urease activity in gastric mucosa is sometimes done if the clinician is looking for *Helicobacter* sp. in the stomach. This bacteria has strong urease activity. To perform this, one or preferably two fresh pieces of gastric mucosa are placed into urease agar and observed for up to 24 hours. If these urease-producing bacteria are present, their enzyme will split the urea in the agar into ammonia and the pH indicator in the agar will change from amber to pink (sometimes this occurs within 15 minutes). Tubes of urease agar may be obtained from microbiologic supply houses. There are also special kits designed to detect *Helicobacter* spp. In dogs and cats there is no good evidence that this test is more advantageous than special staining (e.g., Warthin-Starry) of multiple gastric biopsy specimens.

Intestinal permeability testing can be performed, and finding increased permeability seems to be a reliable marker of small intestinal disease. However, at this time it is impossible to diagnose a patient with increased small intestinal permeability as having a particular disease. Currently, the major value to such testing seems to be (1) determining that a patient with clinical signs of uncertain cause has small intestinal disease and (2) evaluating response to therapy in difficult-to-manage patients. This test is seldom done in clinical cases.

Fecal alpha-1 protease inhibitor can be measured in feces and is a marker for gastrointestinal protein loss. Clinically, this test is rarely indicated but could be helpful when trying to distinguish whether hypoalbuminemia is at least partly due to a protein-losing enteropathy in a patient with known renal protein loss or hepatic insufficiency.

Tests for *Pythium insidiosum* are available. ELISA tests for antibodies and PCR testing for antigen can be done at Louisana State University (Dr. Amy Grooters, College of Veterinary Medicine, Lousiana State University, Baton Rouge, LA 70803).

### **ENDOSCOPY**

Endoscopy is often cost-effective if radiographic and ultrasonographic findings have been nondiagnostic in animals with chronic vomiting, diarrhea, or weight loss. It permits rapid exploration of selected sections of the alimentary tract and mucosal biopsy without the need for a thoracotomy or laparotomy. Although excellent for detecting morphologic changes (e.g., masses, ulcers, obstruction), it is insensitive for revealing abnormal function (e.g., esophageal weakness).

Rigid endoscopy is easier to perform and less expensive than flexible endoscopy, and it can provide excellent biopsy

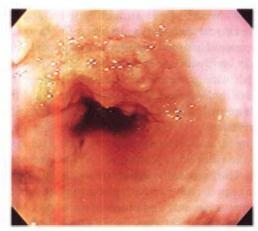


FIG 29-11
Endoscopic view of a polypoid mass in the esophagus of a Chow. This represents an adenocarcinoma.

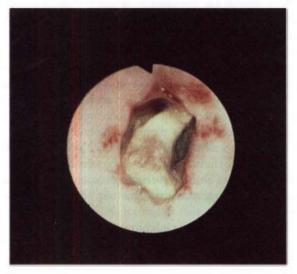


FIG 29-12
Endoscopic view of the esophagus of a dog with a chicken neck bone lodged in it. The bone was ultimately removed with a rigid scope and alligator forceps.

samples. Flexible endoscopes can be used to examine structures that cannot be inspected with a rigid endoscope. Flexible instruments are expensive, and it takes time to become proficient in their use. In addition, one is limited by how far the instrument can be advanced. Furthermore, tissue samples obtained through a flexible endoscope may have artifacts or may be too small to yield diagnostic findings unless the clinician's technique is excellent.

Esophagoscopy is useful in looking for esophageal tumors (Fig. 29-11), foreign objects (Fig. 29-12), inflammation (Figs. 29-13 and 29-14), and obstructions caused by cicatrix (Fig. 29-15). Foreign objects and cicatrix are preferentially treated endoscopically. Esophagoscopy may also show partial obstructions not detected by contrast esophagrams. It is important in such procedures to enter the stomach and retroflex the scope's tip to view the lower esophageal sphinc-

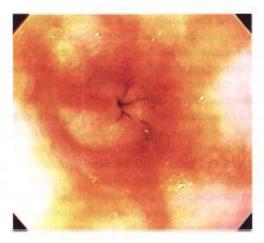


FIG 29-13
Endoscopic view of the lower esophageal sphincter of a dog with moderately severe reflux esophagitis secondary to vomiting. Note the hyperemic areas.

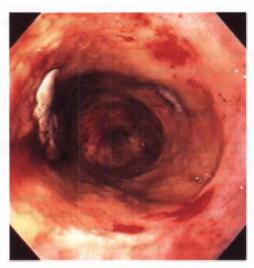
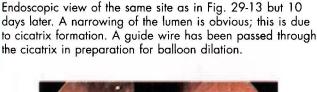


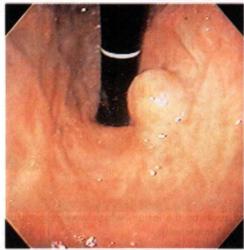
FIG 29-14
Endoscopic view of the distal esophagus of a dog with severe esophagitis secondary to a bone foreign body. Note the white plaque in the 9 o'clock position that is due to pressure necrosis from the foreign body.

ter area to detect leiomyomas (Fig. 29-16) or other easily missed lesions. The esophageal lumen is covered with squamous epithelium, which cannot be pulled off with typical flexible endoscopic forceps. Therefore, if esophageal mucosal biopsy specimens are desired, flexible endoscopes are typically inadequate unless the distal feline esophagus is being biopsied or there is a tumor.

Although esophagoscopy may occasionally detect esophageal weakness (Fig. 29-17), it is not sensitive for detecting this and other selected disorders (e.g., diverticula). Not all foreign objects can be safely removed endoscopically, and the clinician must guard against rupturing a diseased esophagus while trying to extract a foreign object. Finally, care must be taken to avoid creating a potentially fatal gastric distention in patients with esophageal strictures and a fatal







View of the lower esophageal sphincter (as seen from the stomach) of a dog with a leiomyoma. This lesion was causing vomiting and regurgitation and would easily have been missed if a careful, methodical examination had not been carried out.

tension pneumothorax in animals with an esophageal perforation.

Rigid endoscopy is often more useful than flexible endoscopy in removing esophageal foreign objects. The rigid endoscope can protect the esophagus during extraction of the object, and it allows the use of rigid forceps that can grasp the foreign object more tightly. Care must be taken to maintain the animal's esophagus as straight as possible when using a rigid endoscope. If a flexible endoscope is used, it is often helpful to pass it through a rigid scope or tube that has been passed through the cricopharyngeal sphincter; this



FIG 29-17 Endoscopic view of a dog with a megaesophagus. Note that the lumen is dilated and there is substantial food material accumulation.

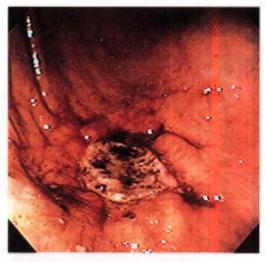


FIG 29-18 Endoscopic view of a gastric ulcer on the greater curvature in a Chow. Note that it is obvious that the mucosa is eroded to the level of the submucosa.

may facilitate passage of the foreign object through the sphincter.

Gastroduodenoscopy and biopsy are indicated in selected animals with vomiting, apparent upper gastrointestinal blood loss, apparent gastroduodenal reflux, or small intestinal disease. It is more sensitive and specific than radiography for detecting mucosal ulcers (Fig. 29-18), erosions (Fig. 29-19), tumors (Fig. 29-20), and inflammatory lesions (Figs. 29-21 to 29-23). Endoscopy is also quicker and less stressful to the animal than exploratory laparotomy. Many foreign objects in the upper gastrointestinal tract (Fig. 29-24) can be removed using endoscopy, and multiple biopsy specimens can be obtained. Occasionally, unexpected diagnoses (e.g., Physaloptera infection; Fig. 29-25) may be found. It may be

Endoscopic view of the gastric mucosa of a dog's stomach that has obvious bleeding. This dog had received nonsteroidal drugs, and the bleeding represented erosions that could not be detected with radiographs or ultrasonography. (From Fossum T, editor: Small animal surgery, St Louis, 1997, Mosby.)

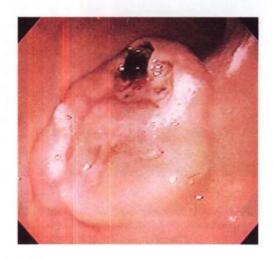
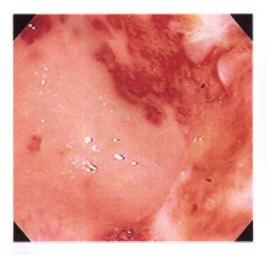


FIG 29-20

Endoscopic view of the stomach of a dog with an obvious mass in the greater curvature. This is an ulcerated leiomyosarcoma that was successfully removed.

necessary to use endoscopes with outer diameters of 9 mm or less in dogs and cats weighing less than 4 to 5 kg. Whenever possible, a scope with a 2.8-mm biopsy channel should be used to obtain larger specimens and allow the use of better foreign object retrieval devices.

The stomach must be as empty as possible when gastroduodenoscopy is performed, which usually necessitates at least a 24-hour fast; many animals undergoing gastroscopy may not empty their stomachs as rapidly as they normally would. During the procedure the stomach must be adequately inflated with air to allow thorough evaluation of its mucosa. Suction must be available to remove secretions or



Endoscopic view of the stomach of a cat with diffuse inflammation, erosion, and ulceration of unknown cause.



A focal gastritis near the pylorus of a dog. Note the reddened spots on the lesion, which were responsible for intermittent hematemesis.

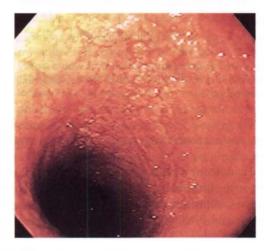


FIG 29-23

The duodenum of a dog with marked inflammatory bowel disease. Note the pseudomembrane-like appearance, which suggests severe disease.

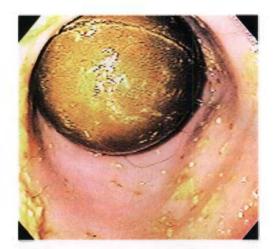


FIG 29-24
Endoscopic view of the antrum of a dog with a ball foreign object that has been present for months and was not detected on plain radiographs or by ultrasonography.

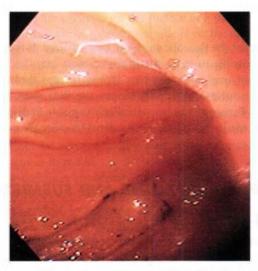


FIG 29-25
Endoscopic view of the greater curvature of the stomach of a dog with a *Physaloptera* attached.

air. The endoscopist must inspect the mucosa methodically to keep from missing lesions. It is particularly easy to miss lesions (e.g., ulcers or *Physaloptera*) just inside the pylorus. Biopsy specimens of the gastric and duodenal mucosa should always be obtained because normal findings seen on visual examination do not rule out the presence of severe mucosal disease. Like esophagoscopy, gastroscopy is not sensitive in identifying functional problems (i.e., gastric hypomotility).

Proctoscopy or colonoscopy is indicated in dogs and cats with chronic large bowel disease unresponsive to appropriate dietary, antibacterial, or anthelmintic therapies as well as those that are losing weight or are hypoalbuminemic. Colonoscopy is more sensitive and definitive, yet comparable in cost to plain and contrast-enhanced radiography. Proctoscopy is used in animals with obvious rectal abnormalities (e.g., stricture felt on digital rectal examination). Rigid



FIG 29-26
Endoscopic view of a normal colon in a dog, showing typical submucosal blood vessels. Inability to see such blood vessels may suggest inflammatory infiltrates.

biopsy forceps obtain excellent tissue samples, which allows the identification of most lesions, including submucosal ones. Biopsy instruments used with flexible endoscopes do not obtain as deep a biopsy specimen but are adequate for obtaining specimens from mucosal lesions.

Proctoscopy and colonoscopy are easier to perform, require less animal restraint, and do not always require the more expensive flexible equipment demanded by other endoscopic procedures. The colon must be clean to allow proper inspection of the mucosa. All food should be withheld for at least 24 and preferably 36 hours before the procedure, a mild laxative (e.g., bisacodyl) should be administered the night before the procedure, and several copious warm water enemas should be given the night before and the morning of the procedure. Proctoscopy requires less cleaning than colonoscopy. Commercial intestinal lavage solutions (e.g., GoLytely, Colyte) clean the colon better than enemas and are particularly useful in larger dogs, those that will be undergoing ileoscopy (which necessitates a very clean ileocolic area), and animals in pain that resist enemas. The lavage solution is usually given to the animal twice the night before the procedure and perhaps once the morning of the procedure. In rare cases, it can cause gastric dilation or volvulus.

Sedation plus manual restraint can often be used instead of anesthesia; however, many animals undergoing colonoscopy have colonic or rectal irritation, and anesthesia is usually preferred. Suction should be available.

Normal colonic mucosa is smooth and glistening, and the submucosal blood vessels can be seen (Fig. 29-26); enema tubes may cause linear artifacts. The colon should distend to a uniform diameter, but it may have bends. If a flexible scope is used, the clinician should identify and inspect the ileocolic valve and the cecum (Figs. 29-27 and 29-28). The clinician should always biopsy the mucosa; normal gross findings do

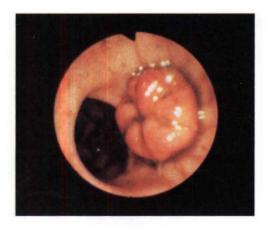


FIG 29-27
Normal ileocolic valve region in a dog. The ileocolic valve is the mushroomlike structure, and the opening below it is the cecocolic valve.

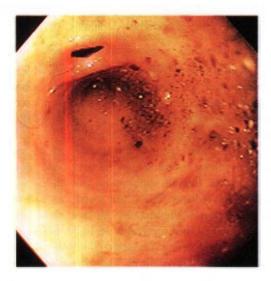


FIG 29-28
Endoscopic view of a normal ileocolic valve region from a cat. The blind pouch is the cecum, and the small opening above it is the ileocolic valve.

not rule out the presence of significant disease. Strictured areas with relatively normal-appearing mucosa are usually caused by a submucosal lesion, in which case biopsying must be aggressive enough to ensure that submucosal tissue is included in the specimen. Cytology can detect histoplasmosis, protothecosis, some neoplasms, and eosinophilic colitis.

An adult or a pediatric human sigmoidoscope is usually adequate for rigid colonoscopy. The tip of the rigid biopsy forceps should have a shearing action (i.e., one part of the tip should fit into the other when it is closed, thus acting like a pair of scissors) instead of a clamshell (also called "double spoon") action in which the edges of the top and bottom jaws simply meet.

Ileoscopy is principally indicated in dogs with diarrhea and in cats with vomiting or diarrhea. It is performed during flexible colonoscopy and requires thorough colonic cleans-

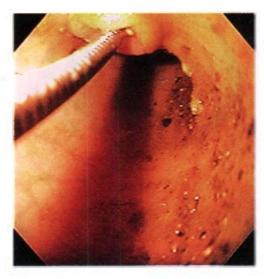


FIG 29-29
Same site as in Fig. 29-28. A biopsy instrument has been blindly passed into the ileum because the scope cannot be advanced through the narrow orifice.

ing so that the ileocolic valve can be visualized. It is difficult or impossible to enter the ileum of most cats (because of size), but one can often pass biopsy forceps through the ileocolic valve and blindly biopsy the ileal mucosa (Fig. 29-29). Ileoscopy can be particularly valuable in diagnosing lymphoma in cats when the duodenal biopsies are nondiagnostic.

# **BIOPSY TECHNIQUES AND SUBMISSION**

# FINE-NEEDLE ASPIRATION BIOPSY

Fine-needle aspiration or core biopsy of enlarged lymph nodes, abdominal masses, and infiltrated abdominal organs may be guided by abdominal palpation or ultrasonography. A 23- to 25-gauge needle is typically used so that any inadvertent intestinal or vascular perforation is insignificant (see Chapter 75).

### **ENDOSCOPIC BIOPSY**

Rigid endoscopy usually provides excellent biopsy samples of the descending colon (i.e., large specimens that include the full thickness of the mucosa, including some muscularis mucosa), but the stomach and small intestine cannot be biopsied with this equipment. Flexible endoscopes can reach more of the alimentary tract, but the tissue samples obtained with these scopes may not always be deep enough to allow submucosal lesions to be diagnosed. Ideally, the tissue to be biopsied is visualized; however, the clinician may pass the biopsy forceps through the pylorus or ileocolic valve and biopsy the duodenum or ileum blindly if the tip of the endoscope cannot be advanced into these areas.

Not all laboratories are adept at processing and interpreting these samples. Endoscopes with 2.8-mm biopsy channel are generally preferred to those with a 2.0- or a 2.2-mm

channel because the larger forceps allow retrieval of substantially larger and deeper tissue samples.

When intestinal or gastric mucosa is biopsied, the tissue sample must be handled carefully to minimize artifacts and distortion. The tissue should be carefully removed from the biopsy forceps with a 25-gauge needle. A squash preparation of one tissue specimen can be evaluated cytologically, and the remaining samples are fixed in formalin and evaluated histologically. The cytology slides should be evaluated by a pathologist familiar with gastrointestinal cytology. Cytologic preparations of the gastric mucosa may show adenocarcinoma, lymphoma, inflammatory cells, or large numbers of spirochetes (see Fig. 32-1). Cytologic studies of the intestinal mucosa may show eosinophilic enteritis, lymphoma, histoplasmosis, or protothecosis, and occasionally giardiasis, bacteria, or Heterobilharzia ova. The absence of cytologic findings suggestive of these disorders does not rule them out, but finding them cytologically is diagnostic.

The laboratory should be consulted regarding the proper way to submit endoscopic tissue sections. In the author's lab, the samples are oriented on the surface of a plastic cassette sponge such that the submucosal side is on the sponge and the luminal side is away from the sponge. The sponge is placed in 10% neutral buffered formalin with the tissues down in the formalin. The clinician should place tissues from different locations in different vials of formalin; each vial should be properly labeled so that the pathologist can correctly identify the area evaluated. Small tissue samples should not be allowed to dry out or be damaged before placement in formalin.

Two common problems with endoscopically obtained tissue samples are that the sample is too small or there is excessive artifact. Lymphomas are sometimes relatively deep in the mucosa (or are submucosal), and a superficial biopsy specimen may then show only a tissue reaction above the tumor, resulting in a misdiagnosis of inflammatory bowel disease. Multiple biopsy specimens should be obtained until there are at least five to eight samples of excellent size and depth (i.e., the full thickness of mucosa). It is important to contact the pathologist and determine whether the quality of the tissue samples was adequate and if the severity of the histologic lesions found is consistent with the clinical signs.

### **FULL-THICKNESS BIOPSY**

If endoscopy is not available, abdominal surgery may be needed to perform gastric and intestinal biopsies. Full-thickness biopsy specimens obtained surgically can have fewer artifacts than those obtained endoscopically; however, the clinician must consider the pros and cons of surgery in a potentially debilitated or ill animal. Endoscopy allows the clinician to direct the biopsy forceps to lesions that cannot be seen from the serosal surface. If surgery is performed, maximal benefit should be obtained from the procedure; the entire abdomen should be examined (i.e., literally from the beginning of the stomach to the end of the colon with all parenchymal organs). Biopsy specimens should be obtained from all obviously abnormal structures. Biopsy specimens of

the stomach, duodenum, jejunum, ileum, mesenteric lymph nodes, and liver (and the pancreas in cats) should be obtained, regardless of how normal these organs appear, unless an obvious lesion is found (e.g., a large tumor). However, it is wise not to assume that a grossly impressive lesion is responsible for the clinical signs; rather, the clinician should perform a biopsy even when the diagnosis seems obvious. Dehiscence is a concern if the serum albumin concentration is less than 1.5 g/dl, but the use of nonabsorbable suture material and serosal patch grafting over intestinal suture lines minimizes the risk. The clinician should consider whether gastrostomy or enterostomy feeding tubes should be placed in emaciated animals before exiting the abdomen.

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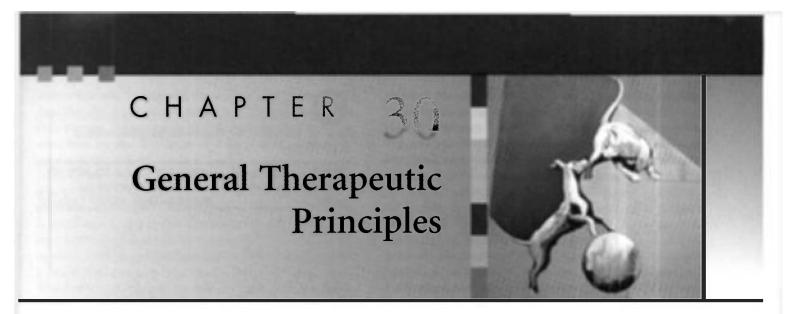
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# CHAPTER OUTLINE

FLUID THERAPY DIETARY MANAGEMENT

Special Nutritional Supplementation
Diets for Special Enteral Support
Parenteral Nutrition
ANTIEMETICS
ANTACID DRUGS
INTESTINAL PROTECTANTS
DIGESTIVE ENZYME SUPPLEMENTATION
MOTILITY MODIFIERS
ANTIINFLAMMATORY AND ANTISECRETORY DRUGS
ANTIBACTERIAL DRUGS
PROBIOTICS/PREBIOTICS
ANTHELMINTIC DRUGS
ENEMAS, LAXATIVES, AND CATHARTICS

# **FLUID THERAPY**

Fluid therapy is primarily used to treat shock, dehydration, and electrolyte and acid-base disturbances. Accurately predicting the nature of electrolyte and acid-base changes on the basis of clinical parameters is impossible; therefore serum electrolyte concentrations must be measured. Vomiting gastric contents inconsistently produces a classic hypokalemic, hypochloremic metabolic alkalosis. The loss of intestinal contents classically produces hypokalemia, with or without acidosis, but a hypokalemic, metabolic alkalosis may occur. Vomiting animals are often assumed to be hypokalemic; however, animals with hypoadrenocorticism or anuric renal failure may be hyperkalemic. If electrolytes have not been measured or if fluid therapy must be started before they are available, physiologic saline solution plus 20 mEq potassium chloride per liter is a reasonable therapeutic choice (see Table 30-1), assuming that the fluids are administered at one to two times the maintenance requirement. A lead II electrocardiographic (ECG) tracing may be evaluated to ensure that moderate to severe hyperkalemia is unlikely (see Chapter 55).

It is rarely necessary or appropriate to administer bicarbonate because reexpanding the vascular compartment and improving peripheral perfusion will alleviate lactic acidosis. Bicarbonate is primarily administered in patients with extreme acidosis (e.g., pH < 7.05 or bicarbonate <10 mEq/L) that are in imminent danger of dying. Bicarbonate or lactated Ringer's solution should not be used if alkalosis seems likely (e.g., vomiting of gastric origin).

Parenteral fluid administration is indicated if the animal is significantly hypovolemic or if the absorption of enteral fluids is questionable (e.g., severe intestinal disease, obstruction, vomiting, or ileus). Subcutaneous (SC) fluid administration is acceptable if the animal is not in shock, absorbs the fluids, and accepts repeated SC administration. Multiple SC depots of 10 to 50 ml each are given, depending on the animal's size. Dependent areas should be checked for the presence of unabsorbed fluids before administering more fluid. Severely dehydrated animals may not absorb SC fluids as rapidly as desired, making initial intravenous (IV) administration more effective. IV fluid administration is required in patients that are severely dehydrated or are in shock, even if a venous cutdown is necessary. Intramedullary administration may be used if IV administration is desired but a catheter cannot be established. To do this, a large-bore hypodermic needle or a bone marrow aspiration needle (preferable) can be inserted through the femur (trochanteric fossa), the tibia, the wing of the ilium, or the humerus. Fluids can be administered by the intramedullary route at a maintenance rate or faster. Intraperitoneal administration is acceptable but repletes the intravascular compartment more slowly than IV or intramedullary techniques.

Dogs in shock (e.g., those with tachycardia, poor peripheral perfusion, cool extremities, a prolonged capillary refill time, a weak femoral pulse, and/or tachypnea) may receive 88 ml of isotonic crystalloids per kilogram or more intravenously during the first hour. This "maximum" rate may be exceeded if necessary to reestablish adequate peripheral perfusion; the patient must be closely monitored to determine whether the fluids are being administered appropriately. It is also important to remember that dogs with systemic inflammatory response syndrome (SIRS) initially have brick-red

oral mucous membranes; warm extremities; and a strong, bounding femoral pulse before the signs of classic shock occur. Large dogs in severe shock, such as those with a gastric volvulus, may require two simultaneous 16- to 18-gauge cephalic catheters and IV bags placed in pneumatic compression devices to achieve an adequate flow rate. It is easier to overhydrate cats; the clinician should therefore monitor cats carefully when rapidly administering fluids. In general, the clinician should not exceed 55 ml/kg during the first hour for cats in shock. Lactated Ringer's solution or physiologic saline solution is commonly used for treating shock. However, the clinician must be sure that fluids that are to be administered rapidly for shock do not contain too much potassium because cardiotoxicity can occur.

Hypertonic saline solution (i.e., 7%) may be used to treat severe hypovolemic or endotoxic shock. Relatively small volumes (i.e., 4 to 5 ml/kg delivered over 10 minutes) seem to be as effective as larger volumes of isotonic crystalloids. Hypertonic solutions shift fluid from the intracellular and interstitial compartments into the intravascular compartment and stimulate vascular reflexes. Hypertonic solutions generally should not be used in animals with hypernatremic dehydration, cardiogenic shock, or renal failure. Uncontrolled hemorrhage may also be a contraindication to their use. The clinician may readminister hypertonic saline solution in 2 ml/kg aliquots until a total of 10 ml/kg has been given or until the serum sodium concentration is 160 mEq/ L or more. After administering hypertonic saline solution, the clinician may continue to administer other fluids but at a reduced rate (e.g., 10 to 20 ml/kg/hr) until shock is controlled. A mixture of 7% saline solution plus dextran 70 has a longer duration of action than hypertonic saline solution alone. This combination may be administered at a rate of 3 to 5 ml/kg over 5 minutes. Dextran is rarely associated with allergic reactions or renal failure but should be used carefully or not at all in animals with coagulopathies.

Colloids (e.g., hetastarch) are also useful in treating shock. Like hypertonic saline solution, colloids draw water from the interstitial compartment into the vascular compartment; however, their effects last longer and do not increase the total body sodium load. Relatively small volumes can be administered quickly (i.e., 5 to 10 ml/kg, maximum of 20 ml/kg in 1 day), and the clinician must reduce the subsequent rate of IV fluid administration to prevent hypertension. Colloids should be used with caution in animals with bleeding tendencies.

If it is difficult to maintain peak systolic blood pressures above 80 to 90 mm Hg, vasopressors may be needed. Constant rate infusion of vasopressin has been very effective for this purpose, even when dobutamine and dopamine were unsuccessful.

Approximately 44 to 66 ml of fluid per kilogram of body weight is required daily for maintenance for dogs weighing between 10 and 50 kg, with larger dogs needing less than smaller dogs. Dogs weighing less than 5 kg may need 80 ml/kg/day. It is important to choose the correct fluid to prevent electrolyte imbalances, especially hypokalemia. In general,



General Guidelines for Potassium Supplementation of IV Fluids

PLASMA POTASSIUM CONCENTRATION (mEq/L)	AMOUNT OF KCI TO ADD TO FLUIDS GIVEN AT MAINTENANCE RATES* (mEq/L)
<b>3</b> . <i>7</i> - <b>5</b> .0	10-20
3.0-3 <i>.7</i>	20-30
2.5-3.0	30-40
2.0-2.5	40-60
≤2.0	60-70

<sup>\*</sup>Do not exceed potassium, 0.5 mEq/kg/hr, except in animals in hypokalemic emergencies and then only with constant, close electrocardiogram (ECG) monitoring. Be sure to routinely monitor plasma potassium concentrations whenever administering fluids with more than 30 to 40 mEq of potassium per liter.

potassium should be supplemented if the animal is anorectic or vomiting, has diarrhea, or is receiving prolonged or intense fluid therapy (see guidelines for administration in Table 30-1). The animal should be monitored for the development of iatrogenic hyperkalemia (e.g., ECG or plasma potassium determinations), and no more than 0.5 mEq/kg/h should generally be administered. Oral (PO) potassium supplementation is often more effective than parenteral supplementation if the animal is not vomiting. Cats receiving IV fluids often show an initial decrease in their serum potassium concentrations, even if the fluids contain 40 mEq or more of potassium chloride per liter.

Dehydrated animals not in shock are treated by replacing the estimated fluid deficit. To do this, first the degree of dehydration must be estimated. Prolonged skin tenting is usually first noted at 5% to 6% dehydration. However, any dog or cat that has lost weight may show skin tenting, whereas obese animals and those with peracute dehydration often do not show skin tenting, regardless of the severity of dehydration. Dry, tacky oral mucous membranes usually indicate 6% to 7% dehydration. However, dehydrated, nauseated animals may have moist oral mucous membranes, whereas wellhydrated, panting, or dyspneic animals have dry mouths. Multiplying the estimated percentage of dehydration by the animal's weight (in kilograms) determines the liters required to replace the deficit. This amount is typically replaced over 2 to 8 hours, depending on the animal's condition. Fluid delivery rate should generally not exceed 88 ml/kg/hr. In general, it is better to slightly overestimate rather than underestimate the fluid deficit, unless the animal has congestive heart failure, anuric or oliguric renal failure, severe hypoproteinemia, severe anemia, or pulmonary edema. It is usually easier to harm cats than dogs by excessive fluid administration.

Ongoing losses are typically estimated from the observation of vomiting, diarrhea, and urination; however, it is common to underestimate losses. Weighing the animal regularly is one way to estimate the adequacy of maintenance fluid therapy. A progressive weight loss suggests inadequate fluid therapy. The same scale should always be used to ensure consistent results. A change of 1 lb (0.45 kg) represents approximately 500 ml of water.

The development of inspiratory pulmonary crackles, a gallop rhythm, or edema (especially cervical) indicates that the animal is probably overhydrated. A new heart murmur is not always a sign of overhydration; severely dehydrated dogs with valvular insufficiency may not have an audible murmur until they are volume replete. The central venous pressure is excellent for detecting excessive fluid administration; however, it is rarely necessary to measure it, except in animals with severe cardiac or renal failure and those receiving aggressive fluid therapy. The central venous pressure (CVP) is normally less than 4 cm H<sub>2</sub>O and generally should not exceed 10 to 12 cm H<sub>2</sub>O, even during aggressive fluid therapy. Poor technique will often give falsely high CVP readings.

Oral rehydration therapy makes use of the facilitated intestinal absorption of sodium. The co-administration of a monosaccharide (e.g., dextrose) or amino acid with sodium speeds up sodium absorption and subsequent water uptake. This approach works if the animal can ingest oral fluids (i.e., it is not vomiting) and the intestinal mucosa is functional (i.e., there is reasonable villus function). Absorption primarily occurs in the mature epithelium near the villus tip. Various products for use in people are commercially available, and there are also recipes for making these solutions. Failure to monitor the patient or follow instructions may lead to the development of severe hypernatremia. Some dogs and cats with acute enteritis not caused by severe parvoviral enteritis can receive rehydration fluids orally.

The type of fluid therapy used in hypoproteinemic animals depends on the degree of hypoalbuminemia. Excessive fluids can dilute the serum albumin concentration, causing ascites, edema, diminished peripheral perfusion, or a combination of these. Careful calculation of the fluid needs and ongoing losses is therefore necessary. In animals with severe hypoalbuminemia (e.g., serum albumin of 1.5 g/dl or less), a plasma transfusion (6 to 10 ml/kg of plasma initially) may be considered to improve the oncotic pressure. A common mistake is to give inadequate amounts of plasma. Therefore the serum albumin concentration should be measured 8 to 12 hours after the transfusion to ensure that sufficient plasma was administered. Further, animals with severe protein-losing enteropathies and protein-losing nephropathies rapidly excrete the supplemented protein, making repeated transfusions necessary if the plasma albumin concentration is to be maintained. It can therefore be very expensive to replenish albumin in large, hypoalbuminemic dogs. Human albumin has been used instead of canine plasma and appears efficacious although side effects have been reported. Hetastarch (5 to 20 ml/kg/day) and dextran 70 may be used in place of plasma or albumin. Hetastarch (supplied as a 6% solution) is larger than albumin and therefore may persist in the intravascular space longer than

albumin, thereby helping maintain the plasma oncotic pressure in animals with severe protein-losing enteropathies. If hetastarch is used, the clinician should decrease the rate of fluid administration to prevent hypertension. Sometimes, administering hetastarch results in massive fluid retention and substantial worsening of ascites.

### DIETARY MANAGEMENT

Symptomatic or specific dietary therapy is often important in animals with gastrointestinal tract problems. Symptomatic therapy usually involves the use of bland, easily digested diets, whereas specific therapy typically involves the use of elimination or hypoallergenic diets, diets with a highly restricted fat content, fiber-supplemented diets, or a combination of these.

Bland, easily digested diets are indicated in animals with acute gastritis or enteritis. Such diets are available commercially (Box 30-1). Homemade versions usually consist of boiled poultry or lean hamburger, low-fat cottage cheese, boiled rice, and/or boiled potatoes in some combination. Boiled chicken, turkey, or fish and green beans may be useful in cats. A typical mixture is one part boiled chicken or cottage cheese and two parts boiled potato. The restricted-fat content facilitates digestion. These diets also tend to be low in lactose, which helps prevent maldigestion. Frequent, small amounts of these foods are usually fed until the diarrhea resolves, and then the diet is gradually changed back to the routine one. This diet may be continued after the event is over; however, if a homemade diet is used long-term, it must be nutritionally balanced (especially for puppies and kittens).

These easily digested diets usually also help prevent vomiting because they are low in fat and fiber (both delay emptying) and high in complex carbohydrates. Extremely hyperosmolar diets should be avoided (e.g., do not use concentrated sugar solutions or honey) because they also may delay gastric emptying.

Elimination diets are indicated if a dietary allergy (i.e., an immune-mediated hypersensitivity to a dietary component) or intolerance (i.e., a nonimmune-mediated problem) is sus-



# Examples of Commercial Bland\* Diets

Hill's Prescription Diet i/d lams Eukanuba Low-Residue-Adult Purina CNM EN-Formula Royal Canin Intestinal HE Formula (dogs) Royal Canin Canine Low Fat

Royal Canin Intestinal HE 30 Formula (cats)

This list is a partial list for the purpose of showing examples of such diets. It is not an all-inclusive list of such diets.

<sup>\*&</sup>quot;Bland" refers to easily digestible diets that often contain less fat than is found in many pet foods.



BOX 30-2

### Examples of Homemade, Hypoallergenic\* Diets

1 part boiled white chicken or turkey meat without the skin; 2 parts boiled or baked potato (without the skin)

1 part boiled or broiled white fish without the skin; 2 parts boiled or baked potato (without the skin)

1 part boiled mutton, venison, or rabbit without the skin; 2 parts boiled or baked potato (without the skin)

1 part drained, low-fat cottage cheese; 2 parts boiled or baked potato (without the skin)

A nonflavored vitamin supplement may be given three times per week.

Rice can be substituted for potato, but many dogs and cats seem to digest potato more easily than rice.

These diets are not balanced but are adequate for 3 to 4 months of use in sexually mature animals. If growing animals are being fed such a diet, then a nutritionist must be consulted to balance calcium and phosphorus.

\* Hypoallergenic refers to a diet specially formulated for a given animal, one that does not expose the animal to potential allergens that it has eaten in the past. Therefore the clinician must obtain a careful dietary history to determine what will or will not constitute a hypoallergenic diet for a particular animal.

pected. There is also evidence that such diets may help treat and control antibiotic-responsive enteropathies. These diets may be composed of the same ingredients found in bland diets; however, they must be formulated so that the animal is fed food that it has not eaten before (and hence could not be responsible for causing allergy or intolerance) or food that is very unlikely to provoke allergy or intolerance (e.g., potatoes). Excellent commercial elimination diets are available, or the clinician may suggest a homemade diet. Examples of homemade elimination diets are described in Box 30-2.

Elimination diets that are going to be effective are usually effective within 3 to 4 weeks, although in rare cases patients may require 6 or more weeks before clinical efficacy is evident. It is critical that no other foods or treats be given to the animal during this time (e.g., flavored pills, toys, medications). If the signs resolve during this time, the diet should be continued for at least 4 to 6 more weeks to ensure that it is the diet that is responsible for the animal's improvement and not a spontaneous fluctuation of the disease. If a homemade diet was used, the clinician should try to gradually switch the animal to a commercial diet or balance the homemade diet with appropriate vitamins, minerals, and fatty acids.

Partially hydrolyzed diets (Purina HA; Nestle Purina, Hill's z/d; Hill's Pet Products, Hypoallergenic HP19 Formula [dogs] and Hypoallergenic HP23 Formula [cats]; Royal Canin) have been formulated in an attempt to eliminate proteins large enough to cause immunologic reactions (i.e., make a diet that is hypoallergenic for all animals). Although these diets are not uniformly effective, many dogs and cats with gastrointestinal diseases will have clinical improvement

when eating these diets exclusively. The partially hydrolyzed proteins may also make such diets easier for diseased alimentary tracts to digest and absorb.

Elemental diets (e.g., Vivonex TEN; Novartis Nutrition) are diets in which the nutrients are supplied as amino acids and simple sugars. These diets are hypoallergenic, but more important, they are extremely easy to digest and absorb when there is major small intestinal disease. Diseased intestines have increased permeability, which allows luminal contents to leak into the mucosa. Such leakage may be an important mechanism perpetuating intestinal inflammation. Because the amino acids and simple sugars found in elemental diets do not elicit an inflammatory reaction when they enter the interstitium, they do not contribute to perpetuation of the inflammatory response in the intestines. The elemental diets prepared for people (e.g., Vivonex TEN) typically have less protein than desired for veterinary patients. Therefore protein supplements are usually given when preparing this diet by adding 350 ml of water plus 250 ml of 8.5% amino acids (for injection) instead of 600 ml of water. Adding 1 to 2 ml of a flavored vitamin syrup often makes it palatable. If the animal will not drink this formulation, it may be administered via nasoesophageal tube. These diets are generally reserved for patients that are extremely ill from severe intestinal disease.

Ultra-low-fat diets are indicated in animals with intestinal lymphangiectasia. Because long-chain fatty acids enter lacteals and are reesterified, removing them from the diet therefore prevents the dilation and rupture of lacteals and the subsequent intestinal lymphatic loss. Medium-chain triglycerides (MCTs) were once recommended as supplements to such diets at a dose of 1 to 2 ml/kg of body weight. MCTs appear to be absorbed into the portal blood without going through the lacteals and thoracic duct. They have an unpleasant taste, so very small amounts (e.g., 1 tsp/lb of food) should be added to the diet initially. Otherwise, the animal may refuse to eat the food. Using a highly digestible, ultra-low-fat diet usually eliminates the need for supplementing MCTs; however, MCTs have been used to help very thin animals with severe gastrointestinal disease absorb nutrients and gain weight.

Fiber supplementation may help many dogs and cats with large (and rarely small) intestinal diseases. Although fiber is generally classified as soluble or insoluble, many fibers have characteristics of both. Insoluble fiber is poorly digested or metabolized by bacteria and ultimately produces more stool bulk. Some insoluble fibers apparently normalize colonic myoelectrical activity and help prevent spasms. Soluble fiber can be metabolized by bacteria into short-chain volatile fatty acids, which are trophic to colonic mucosa; it may also slow the absorption of nutrients by the small intestine.

Fiber-enriched diets may ameliorate diarrhea in many animals with large bowel disease (especially those with minimal inflammation) and lessen constipation not caused by obstruction or pain. Such a diet should be fed for at least 2 weeks before assessing efficacy, although most animals that respond do so within the first week. A commercial high-fiber

diet may be used, or fiber may be added to the current diet. Psyllium hydrocolloid (e.g., Metamucil) or coarse, unprocessed wheat bran may be added to the pet's diet in the amount of 1 to 2 teaspoons or 1 to 4 tablespoons per can of food, respectively. Some cats will not eat these diets or fiber supplements; however, canned pumpkin pie filling is effective and usually acceptable to cats; 1 to 3 tablespoons may be given daily. It is important that the animal maintain adequate water intake, lest the increased dietary fiber produce obstipation. If too much soluble fiber is fed, there may be excessive stool, which the owner then mistakes for continued large bowel disease.

# SPECIAL NUTRITIONAL SUPPLEMENTATION

If the animal refuses to ingest adequate calories, special nutritional supplementation is necessary. Daily nutritional requirements should be calculated to avoid underfeeding. Approximately 60 kcal/kg/day is reasonable for the maintenance needs of mature dogs and cats that are not lactating or losing a significant amount of energy or protein. More exact calculations are recommended if the animal has severe disease or ongoing fluid and nutritional losses (Box 30-3).

In some cases, simply sending the animal home, warming the food, or feeding the animal a palatable diet (e.g., chicken baby food for dogs) ensures adequate caloric intake. The clinician can attempt force-feeding by manually placing food in the animal's mouth, although this seldom works in severely anorectic animals. Cyproheptadine (2 to 4 mg per cat) stimulates some cats to eat, especially those with mild anorexia. However, cyproheptadine seldom induces a severely anorectic cat (e.g., one with severe hepatic lipidosis) to ingest adequate calories. Diazepam rarely causes acute feline hepatic failure. Megestrol acetate is an excellent appetite stimulant but occasionally causes diabetes mellitus, reproductive problems, or tumors. Cobalamin injections have been noted to increase appetite in some dogs. Recently, mirtazapine has been used with anecdotal success in dogs (once daily) and cats (every three days). Appetite stimulants are usually less effective in dogs than in cats.

Tube feeding is a more reliable way to ensure that adequate calories are ingested. Intermittent orogastric tube feeding is useful for animals that need nutritional support for only a relatively short time, although it may be used for longer periods in orphaned puppies and kittens. It is typically done two or three times daily, using restraint and a mouth gag. A tube is measured and marked to correspond to the length from the tip of the nose to the midthoracic region. The tube is then carefully inserted through the mouth gag to the premarked point. If the animal coughs or is dyspneic, the tube may have entered the trachea and should be repositioned. To ensure safety, the clinician should flush the tube with water before the warmed gruel is administered. The gruel should be given over several seconds or 1 minute. Because relatively large-diameter tubes can be used, homemade gruels may be administered in this way. The major



### Calculation of Nutritional Needs and Formulations of Total Parenteral Nutrition Solution

Actual body weight =	kg	
Basal Energy Requirement		
30 (weight in kg) + 70 = $\frac{1}{100}$ kcal/day However, if <2 kg or >25 kg, use 70 (weight in kg) <sup>0.75</sup>		
Maintenance Energy Requirement		
Adjustment factors: Cage rest After surgery Trauma Sepsis Severe burn	Dogs (1.25) (1.3) (1.5) (1.7) (2.0)	Cats (1.1) (1.12) (1.2) (1.28) (1.4)
Basal Requirement × Adjustment Factor =		
		kcal/day
Protein Requirement		
4 g/kg in adult dogs 6 g/kg in cats and hypoproteinemic dogs If there is renal failure, use 1.5 g/kg in dogs or 3 g/kg in cats		
		g/day

Solution formulation:				
g of protein necessitates ml of an 8.5% or				
10% amino acid solution (85 or 100 mg of protein/ml, respectively).				
Determine the calories derived from the protein (4 kcal/g of				
protein), and subtract this from the daily caloric needs. Supply the				
remaining calories with glucose and lipid kcal needed.				
Provide at least 10%, and preferably 40%, of caloric needs with				
lipid emulsion. A 20% lipid emulsion has 2 kcal/ml. Do not use in				
lipemic animals; use with caution in animals with pancreatitis.				
ml needed. Provide remainder of calories with 50%				
dextrose, which has 1.7 kcal/ml ml needed.				
Use one half the calculated amount of solution on the first day, and				
increase it to the calculated amount on the second day, if				
hyperglycemia, lipemia, azotemia, or hyperammonemia does not				
occur.				
Either use amino acid solution with electrolytes or add electrolytes				

Either use amino acid solution with electrolytes or add electrolytes so that the solution has sodium, 35 mEq/L; chloride, 35 mEq/L; potassium, 42 mEq/L; magnesium, 5 mEq/L; and phosphate, 15 mmol/L. These concentrations may be adjusted as needed, depending on the animal's serum electrolyte concentrations. Add multiple vitamins and trace elements (especially zinc and copper) that are formulated for parenteral nutrition solutions. For partial (also called peripheral) parenteral nutrition formulation, see Zsombor-Murray et al: Peripheral parenteral nutrition, Comp Cont Educ 21:512, 1999.

disadvantage is the need to physically restrain the animal. Placement of an indwelling tube (discussed in more detail later in this chapter) circumvents this problem.

Nasoesophageal tubes are indicated in animals that need nutritional support and have a functional esophagus, stomach, and intestines. They are easy to place, but they are difficult to maintain in animals that are vomiting. To place them, the clinician first anesthetizes the nose by instilling a few drops of lidocaine solution in one nostril. Then the clinician lubricates a sterile polyvinyl chloride, polyurethane, or silicone tube (the diameter depends on the animal's size, but 5F to 12F is typical) with sterile, water-soluble jelly and inserts it into the ventromedial portion of the nostril. The animal's head is restrained in its normal position, and the tube is inserted until the tip is just beyond the thoracic inlet. If the clinician encounters difficulty in passing the tube, the tip should be withdrawn, redirected, and advanced again. If the clinician is unsure whether the tube is in the esophagus, thoracic radiographs should be obtained or several milliliters of sterile saline solution should be instilled into the tube to see if this provokes coughing.

Tape is applied to the tube to secure it, and then the tape is glued or sutured as needed to the skin along the dorsal aspect of the nose. The tube must not be allowed to touch sensory vibrissae because the animal will not tolerate it. It may be necessary to place an Elizabethan collar on some animals to prevent them from pulling out the tube. Only small-diameter tubes (e.g., 5F) can be used in small dogs and cats, which limits the rate of administration and necessitates the use of commercial liquid diets (Table 30-2) instead of less expensive homemade gruels. The clinician should flush the tube with water after each feeding to prevent occlusion. Long-term acceptance is typical, but rhinitis occurs in some animals.

Some dogs and cats do not tolerate nasoesophageal tubes and repeatedly pull them out. However, they are usually effective for short-term therapy (e.g., 1 to 10 days), and some animals tolerate them for weeks.



DIET	COMMENTS
Osmolite*	Polymeric diet; contains taurine, carnitine, and MCT
CliniCare†	Polymeric diet; contains taurine, but no lactose
Jevity*	Polymeric diet; contains taurine, fiber, carnitine, and MCT
Peptamen‡	Oligomeric diet; contains taurine, carnitine, and MCT
Pulmocare*	Polymeric diet; contains taurine, carnitine, and MCT
Vital HN*	Oligomeric diet; contains MCT
Vivonex T.E.N.§	Elemental diet; high in carbohydrates, low in protein and fat!

MCT, Medium-chain triglyceride.

Pharyngostomy and esophagostomy tubes are indicated in animals with a functional esophagus, stomach, and intestines that require nutritional support but do not tolerate nasoesophageal or intermittent tube feeding. Vomiting may make it difficult to maintain these tubes, but they can be used for weeks to months.

To place a pharyngostomy tube, the clinician anesthetizes the animal and inserts a finger into the mouth so that the tip of the finger is caudal to the epihyoid bone and as dorsal and as close to the cricopharyngeal sphincter as possible. The tip of the finger is then pushed laterally, and a skin incision is made over this spot. Hemostats are used to bluntly dissect through to the pharynx. A soft latex or rubber catheter (18F to 22F, urinary) is then inserted into the opening and into the esophagus. In general, the tip of the catheter should end in the midthoracic esophagus. The tube is secured with traction sutures and the area bandaged. Some inflammation at the stoma is common, and routine cleansing and bandage changes are necessary. Systemic antibiotics are not typically needed. An Elizabethan collar may be used if the animal tries to remove the tube. To remove the tube, the clinician simply cuts the sutures and pulls it out. The opening will close spontaneously over the next 1 to 4 days. Pharyngostomy tubes effectively bypass oral lesions. Advantages of these tubes include easy placement, easy removal, and minimal complications if they have been properly inserted (i.e., they cannot cause peritonitis as gastrostomy or enterostomy tubes can). However, it is easy to place them such that they cause gagging and regurgitation (i.e., if they touch the larynx, especially in cats and small dogs). The clinician should take care not to disrupt vessels or nerves when using scissors or a scalpel during the dissection. Because pharyngostomy tubes are larger than nasoesophageal tubes, homemade gruels can be fed through them.

The placement of esophagostomy tubes is similar to that of pharyngostomy tubes. The animal is placed in right lateral recumbency, the mouth is held open, and a long right-angle hemostat is placed through the cricopharyngeal sphincter. The tip of the hemostat is then forced up to show where to make the incision in the left cervical region. The incision should be made midway between the cricopharyngeal sphincter and the thoracic inlet. The tip of the hemostat is forced up through the esophagus and the nick in the skin; the tip of a feeding tube is then grasped and pulled into the esophagus and out the mouth so that the flared end of the catheter (i.e., where the syringe will be attached) is left protruding from the neck. The distal end of the catheter is then redirected down the esophagus with a rigid colonoscope or other device. Esophagostomy tubes cannot cause gagging but are otherwise similar to pharyngostomy tubes.

Gastrostomy tubes bypass the mouth and esophagus in animals with a functional stomach and intestines. They can also be used when nasoesophageal, pharyngostomy, esophagostomy, or intermittent gastric tubing is unacceptable. Vomiting is not a contraindication. This technique requires surgery, endoscopy, or special devices for proper placement.

<sup>\*</sup> Ross Laboratories, Columbus, Ohio.

<sup>†</sup> Abbott Animal Health, North Chicago, Ill.

<sup>‡</sup>Nestle Nutrition, Deerfield, III.

<sup>§</sup> Novartis Nutritian, Minneapolis, Minn.

<sup>||</sup> To increase protein content, reconstitute one packet of powder with 350 ml water plus 250 ml of 8.5% amino acids for injection.

Endoscopy is the preferred and safest way to place these tubes percutaneously. The use of dedicated devices for the placement of gastrostomy tubes has made the procedure easier and readily available for clinicians without endoscopes (Fig. 30-1). To place gastrostomy tubes using these devices, the clinician positions the anesthetized animal in right lateral recumbency and surgically prepares the area behind the last rib on the left abdominal wall. The device is then blindly and carefully advanced down the esophagus until the tip is in the stomach and can be seen pushing against the skin behind the last rib. The plunger on the handle is advanced until the trocar in the tip penetrates the skin and can be seen. In the tip of the trocar is a hole in which a suture (e.g., No. 1 or 2 polyamide or other nonabsorbable material) is tied. The clinician then withdraws the device from the animal, bringing one end of the suture with it. In the meantime, another person grasps the other end of the suture firmly so that it cannot be pulled into the stomach. The end of the suture that was brought out through the mouth is now passed retrograde through the sheath of an 18-gauge over-the-needle IV catheter or a disposable pipette tip of similar diameter. Next, one can use either an umbrella catheter specifically designed for use as a gastrostomy tube, or one can modify a mushroom-type catheter (usually 18F to 24F). The latter is prepared by cutting off the syringe end. The clinician then attaches the suture that has been pulled out through the mouth to this end of the catheter, using a needle to pass the suture through the catheter and make a mattress suture pattern. The end of the mushroom catheter tip that has just been attached to the suture is inserted into the flared end of the IV catheter or disposable pipette tip. The other person then begins to pull on the end of the suture where it enters the abdominal wall, thus pulling the cut tip of the mushroom catheter into the stomach. The modified end of the mushroom catheter that was inserted into the disposable pipette tip is thereby pulled out of the stomach through the same hole previously made by the trocar. Traction is placed on the mushroom catheter until the mushroom head is securely placed against the gastric mucosa, which is pulled next to the abdominal wall. (The clinician should take care not to pull the mushroom tip of the catheter out of the stomach.) The catheter is held in place by an outer flange and/or traction sutures (excessive pressure on the gastric mucosa can cause avascular necrosis), and the area is bandaged lightly.

Gastrostomy tubes allow the administration of thick gruels and are often tolerated for weeks to years. Either a homemade gruel or a commercial liquid diet (see Table 30-2) may be used. These tubes must be left in place for at least 7 to 10 days to allow an adhesion to form between the stomach and the abdominal wall, which will prevent gastric leakage into the peritoneal cavity when the tube is removed. They are often used in cats that do not tolerate pharyngostomy, nasogastric, or esophagostomy tubes. The tube should be flushed with water and air after each feeding. Although the entire caloric requirement may be administered as soon as the tube is placed, it is often better to start with one half the

daily requirement and work up to the complete nutritional needs over 1 to 3 days. If the tube becomes plugged, it can sometimes be unplugged by using flexible endoscopy forceps or by instilling a fresh carbonated beverage into the tube. When the tube is to be removed, sufficient traction is applied to the catheter so that the mushroom tip collapses and passes through the stomach and skin incision. The fistula usually closes spontaneously in 1 to 4 days. The major risk of using such tubes is leakage and peritonitis, which are rare but potentially catastrophic. In dogs larger than 20 to 25 kg, gastrostomy tubes are typically placed surgically or sutures are passed through the abdominal wall and into the gastric wall to ensure that the stomach and abdominal wall stay in apposition and form an adhesion that prevents leakage. Improper use of dedicated devices can result in malplacement of the tube and/or perforation of abdominal organs (e.g., spleen, omentum).

Low-profile gastrostomy tubes can be used if a stoma has been previously established by a routine gastrostomy tube. The major advantage of such tubes is that they may replace routine gastrostomy tubes that are disintegrating or have been inadvertently pulled out, and they may be placed without anesthesia or a surgical/endoscopic procedure. Typically, sedation is all that is needed. However, to use the preexisting stoma, the low-profile gastrostomy tube must be placed within 12 hours of removing the old gastrostomy tube, or another tube (e.g., a red latex male urinary catheter) must be inserted into the stoma as quickly as possible to prevent the old stoma from closing.

Enterostomy tubes are indicated in animals with functional intestines when the stomach must be bypassed (e.g., recent gastric surgery). Laparotomy or laparoscopy is generally needed to place these tubes. A 12-gauge needle is used to puncture the antimesenteric border of the intestine, and a sterile 5F plastic catheter is advanced aborally through the needle until approximately 15 cm extends into the intestinal lumen. The 12-gauge needle is removed, and a purse-string suture is placed to prevent the catheter from moving freely. The needle is then used in the same manner to make a pathway for the catheter to exit through the abdominal wall. The antimesenteric border of the intestine is sutured to the abdominal wall so that the sites where the tube enters the intestine and exits the abdomen are opposed. Traction sutures are used to secure the catheter.

The clinician may place a jejunostomy tube by first placing a gastrostomy tube and then inserting a jejunostomy tube through the gastrostomy tube. Next, the clinician directs the jejunostomy tube into the duodenum with a flexible endoscope. Alternatively, the clinician may use a guide wire placed in the duodenum via an endoscope to feed the jejunostomy tube through the gastrostomy tube and into the duodenum.

The small diameter of enterostomy tubes often necessitates the administration of commercial liquid diets (see Table 30-2), which are best infused at a constant rate. The rate necessary to administer daily caloric needs is calculated. A one half-strength feeding solution is administered at one

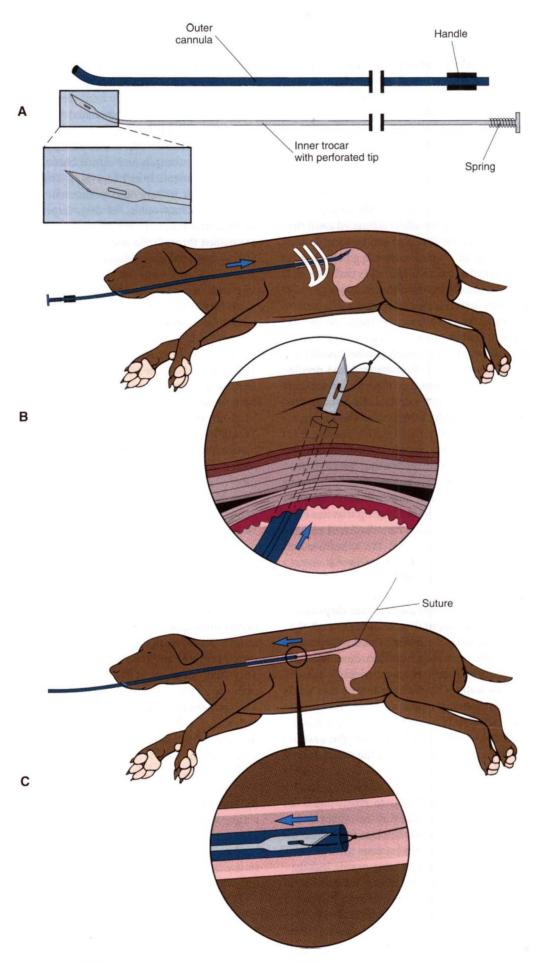
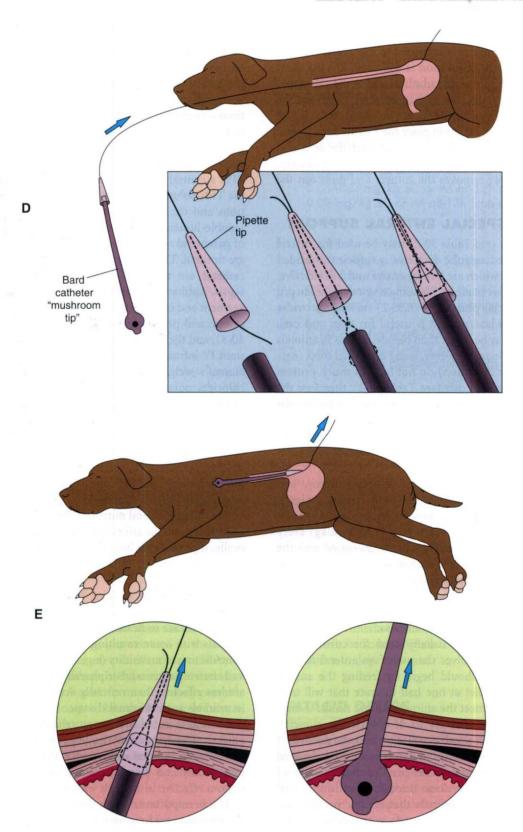


FIG 30-1 For legend see opposite.



# FIG 30-1

The proper way to use a dedicated device to place a gastrostomy tube. **A,** The device consists of a cannula with a handle and a trocar that is passed through the cannula once it is properly positioned. **B,** Proper placement of the device behind the last rib. The trocar is pushed through the cannula until the tip exits the skin such that a suture can be tied onto the tip. **C,** The device and the attached suture are withdrawn through the animal's mouth. **D,** The proper way to use a dedicated device to place a gastrostomy tube. The tip of the suture that exits the mouth is attached to the cut end of a mushroom-tip catheter. **E,** The other end of the suture is pulled so that the tip of the catheter exits the skin. It is pulled until the mushroom tip is snugly against the gastric mucosa and the stomach is held against the abdominal wall. (Reprinted with permission from Fossum T, editor: *Small animal surgery*, St Louis, 1997, Mosby.)

half the calculated rate on the first day. On the second day the rate of administration is increased to the calculated rate, but a one half–strength solution is still used. On the third day a full-strength solution is administered at the calculated rate. If diarrhea occurs, the rate of administration can be decreased or fiber (e.g., psyllium) can be added to the liquid diet. The tube should be left in place for 7 to 10 days, if possible, to allow adhesions to develop around the area and prevent leakage. When enteral feeding is no longer necessary, the clinician simply removes the sutures and pulls out the catheter.

### DIETS FOR SPECIAL ENTERAL SUPPORT

Commercial diets (see Table 30-2) may be used for enteral support. If the feeding tube diameter is sufficient, blended commercial diets, which are less expensive and still effective, can be used. A gruel made by blending one can of feline p/d (Hill's Pet Products) plus 1½ C (0.35 L) of water provides approximately 0.9 kcal/ml and is useful for dogs and cats. Elemental diets may be better than blended gruels in animals with intestinal disease. However, some elemental diets (e.g., Vivonex, Novartis Nutrition) do not have as much protein as desired for dogs and cats (see Table 30-2); therefore the clinician may replace some of the water used in mixing the elemental diet with 8.5% amino acids for injection (e.g., 350 ml water +250 ml 8.5% amino acids). When feeding cats, the clinician must be sure that sufficient taurine is present in the diet.

Nasoesophageal, pharyngostomy, esophagostomy, and gastrostomy tubes are usually used for bolus feeding. Animals that have been anorectic for days to weeks should usually start by receiving small amounts (e.g., 3 to 5 ml/kg) every 2 to 4 hours. The amount is gradually increased and the frequency decreased until the animal is receiving its caloric needs in three or four daily feedings. The clinician should expect to ultimately administer at least 22 to 30 ml/kg at each feeding to most dogs and cats. Larger volumes may be given if they do not cause vomiting or distress.

Enterostomy tubes are usually used for constant-rate feeding, which best involves the use of an enteral feeding pump. The clinician should begin by feeding the animal a one half-strength diet at one half the rate that will ultimately be needed to meet the animal's caloric needs. If diarrhea does not result after 24 to 36 hours, the clinician increases the flow rate to what will ultimately be needed. If diarrhea still does not occur, the diet may then be changed from one half strength to full strength. Constant infusion of these same diets may be done through gastrostomy and esophagostomy tubes in animals that readily vomit when fed food in boluses (e.g., some cats with severe hepatic lipidosis). Animals that are critically ill and vomit readily are believed to potentially benefit from "microalimentation," in which very small amounts of liquid diet (e.g., 1 to 2 ml/h in 30 to 40 kg dogs) are infused into nasoesophageal tubes in an effort to get some nutrition to the intestinal mucosa and prevent bacterial translocation and, ultimately, sepsis.

### PARENTERAL NUTRITION

Parenteral nutrition is indicated if the animal's intestines cannot reliably absorb nutrients. It is the most certain method of supplying nutrition to such animals; however, it is expensive and can be associated with metabolic and infectious complications. There are two types of parenteral nutrition: total parenteral nutrition (TPN) and partial (also called peripheral) parenteral nutrition (PPN). In general, PPN is much more convenient and less expensive than TPN. For TPN a central IV line is dedicated to the administration of the TPN solution only (i.e., the piggybacking of other solutions and the obtaining of blood samples are forbidden). Double-lumen jugular catheters allowing the administration of parenteral nutrition and fluids through the same catheter are optimal. The aseptic placement and management of the catheter are the best protection against catheter-related sepsis. Antibiotic prophylaxis does not replace proper management and is ineffective in preventing infections. The daily caloric and protein requirements are determined (see Box 30-3), and the customized solution is administered by constant IV infusion. The clinician must routinely monitor the animal's weight; rectal temperature; and serum sodium, chloride, potassium, phosphorus, and glucose concentrations (in addition to the urine for glucosuria). The feeding solution is adjusted to prevent or correct serum imbalances. PPN is similar but (1) supplies only approximately 50% of caloric needs, (2) has a lower osmolality than TPN solutions so that peripheral IV catheters are sufficient, and (3) is intended to be used for approximately a week with the goal to get a severely ill or emaciated patient "over the hump" before starting enteral nutrition. Regardless of whether TPN or PPN is used, the animal should also receive some feedings orally, if possible, to help prevent intestinal villous atrophy.

# **ANTIEMETICS**

Antiemetics are indicated for symptomatic therapy in many animals with acute vomiting or those in which vomiting is contributing to morbidity (e.g., discomfort or excessive fluid and electrolyte losses). Peripherally acting drugs (Table 30-3) are less effective than centrally acting ones but may suffice in animals with minimal disease. Some of these drugs are given orally, but this is an unreliable route in nauseated animals. Parasympatholytics (e.g., atropine, aminopentamide) have been used extensively. Although they are given parenterally and may have some central activity, they are seldom effective in animals with severe vomiting.

If it is important to halt the vomiting, a centrally acting drug should be administered parenterally. Suppositories are convenient, but their absorption is erratic.

Phenothiazine derivatives (e.g., prochlorperazine [Compazine]) are often effective. They inhibit the chemoreceptor trigger zone and, in higher doses, the medullary vomiting center. Antiemesis is usually achieved at doses that do not produce marked sedation. However, these drugs may cause vasodilation and can decrease peripheral perfusion in a



DRUG

### Selected Antiemetic Drugs

# **Peripherally Acting Drugs**

Kaopectate/bismuth subsalicylate (poorly effective) Anticholinergic drugs (modest efficacy) Propantheline (Pro-Banthine) Aminopentimide (Centrine)

### **Centrally Acting Drugs**

Phenothiazine derivatives Chlorpromazine (Thorazine) Prochlorperazine (Compazine) Metoclopramide (Reglan)

Serotonin receptor antagonists Ondansetron (Zofran) Dolasetron (Anzemet) Granisetron (Kytril) Neurokinin-1 receptor antagonist Maropitant (Cerenia) Trimethobenzamide (Tigan) (poorly effective) Antihistamine Diphenhydramine (Benadryl) (poorly effective) DOSAGE\*

1-2 ml/kg PO q8-24h (dogs only)

0.25-0.5 mg/kg PO q8-12h 0.01-0.03 mg/kg SC or IM q8-12h (dogs only) 0.02 mg/kg SC or IM q8-12h (cats only)

0.3-0.5 mg/kg IM, IV, or SC q8h 0.1-0.5 mg/kg IM q8-12h 0.25-0.5 mg/kg PO, IM, or IV q8-24h 1-2 mg/kg/day, constant IV infusion

0.1-0.2 mg/kg IV q8-24h 0.3-1.0 mg/kg SC or IV q24h 0.1-0.5 mg/kg PO (anecdotal, dogs only)

1 mg/kg SC q24h or 2 mg/kg PO q24h (dogs only) 3 mg/kg, IM q8h (dogs only)

2-4 mg/kg PO q8h 1-2 mg/kg IV or IM q8-12h

dehydrated animal. Some data suggest that phenothiazines may lower the seizure threshold in animals with epilepsy, but this is uncertain.

Metoclopramide (Reglan) inhibits the chemoreceptor trigger zone and increases gastric tone and peristalsis, both of which inhibit emesis. Rarely, animals show unusual behavior after administration. The drug is excreted in the urine, and severe renal failure makes adverse effects more likely. It rarely worsens vomiting, perhaps because it causes excessive gastric contractions. The liquid form of metoclopramide given orally is often not accepted by cats. Because of its prokinetic activity, the drug is contraindicated in animals with a gastric or duodenal obstruction. Metoclopramide may be more effective in animals with severe vomiting if given intravenously at a dosage of 1 to 2 mg/kg/day by constant rate infusion.

Ondansetron (Zofran) and dolasetron (Anzemet) are serotonin receptor antagonists. Developed for use in people with vomiting resulting from chemotherapy, they are often effective in animals in which vomiting is not controlled with phenothiazines or metoclopramide (e.g., severe canine parvoviral enteritis). Granisetron (Kytril) has been used when an oral medication is required, but its efficacy is uncertain.

Maropitant (Cerenia) is a neurokinin-1 receptor antagonist that has recently been approved for use in dogs. Preliminary data suggest that this will be a useful drug in clinical practice.

Narcotics, such as fentanyl, oxymorphone, and butorphanol, may cause vomiting initially, but vomiting is usually inhibited once the drug penetrates to the medullary vomiting center. Trimethobenzamide (Tigan) and antihistamines are effective in some animals but generally are unreliable antiemetics in dogs and cats.

# ANTACID DRUGS

Antacid drugs (Table 30-4) are indicated when appropriate to lessen gastric acidity (e.g., ulcer disease; acid hypersecretion resulting from renal failure, mast cell tumor, or gastrinoma). Although they are not antiemetics, they apparently may have an "antidyspepsic" effect due to diminishing gastric hyperacidity.

Antacids, which titrate the gastric acidity, are over-thecounter preparations that are typically of limited efficacy because of the way they are administered. Compounds containing aluminum or magnesium tend to be more effective and do not cause the gastric acid rebound that sometimes occurs in response to calcium-containing antacids. Antacids should be administered orally every 4 to 6 hours

PO, Orally; SC, subcutaneously; IM, intramuscularly.

<sup>\*</sup> Dosages are for both dogs and cats unless otherwise specified.

<sup>†</sup>This drug contains salicylate and can be nephrotoxic if combined with other nephrotoxic drugs.

**DRUG** 



Acid Titrating Drugs	
Aluminum hydroxide (many names)	10-30 mg/kg PO q6-8h
Magnesium hydroxide (many names)	5-10 ml PO q4-6h (dogs) q8-12h (cats)
Gastric Acid Secretion Inhib	pitors
H <sub>2</sub> receptor antagonists	
Cimetidine (Tagamet)	5-10 mg/kg PO, IM, ar IV q6-8h
Ranitidine (Zantac)	1-2 mg/kg PO or IV q8-12h (dogs)
	2.5 mg/kg IV or 3.5 mg/kg PO q12h (cats)
Nizatidine (Axid)	2.5-5 mg/kg q24h PO

DOSAGE\*

Pepcid AC)
Proton Pump Inhibitors

Famotidine (Pepcid,

Omeprazole (Prilosec) 0.7-1.5 mg/kg PO q12-24h (dogs)

(dogs)

q12-24h§

0.5 mg/kg PO or IV

Lanosprazole (Prevacid) 1 mg/kg IV q24h (dog)†
Pantoprazole (Protonix) 1 mg/kg IV q24h (dog)†

to ensure continued control of gastric acidity; however, this may cause diarrhea, especially in animals receiving magnesium-containing compounds. Hypophosphatemia, although unlikely, is possible after extensive aluminum hydroxide administration. Hypermagnesemia, also unlikely, is possible in dogs and cats with renal failure that are given magnesium-containing compounds. These types of antacids may also interfere with the absorption of some other drugs (e.g., tetracycline, cimetidine).

Histamine<sub>2</sub> (H<sub>2</sub>) receptor antagonists are indicated when controlling gastric acidity is important. They act by preventing histamine from stimulating the gastric parietal cell. Cimetidine (Tagamet) is effective but should be given three or four times per day to achieve best results; it inhibits hepatic cytochrome P-450 enzymes, thereby slowing the metabolism of some drugs. Famotidine (Pepcid) and nizatidine (Axid) are as or more effective than cimetidine when administered one or two times per day and do not affect hepatic enzyme activity as much as cimetidine does. It is not clear that ranitidine is effective in dogs. The H<sub>2</sub> receptor

antagonists are now available as over-the-counter preparations. The main indication for these drugs is the treatment of gastric and duodenal ulcers. Some clinicians use them prophylactically in an attempt to prevent ulceration associated with the use of some steroids and some nonsteroidal antiinflammatory drugs (NSAIDs), but they are most effective in treating existing ulcers after NSAID or steroid therapy has ceased. They are effective in lessening ulceration associated with submaximal exertion. Nizatidine and ranitidine have gastric prokinetic activity. Very rarely, these drugs may cause bone marrow suppression, central nervous system problems, or diarrhea. Parenteral administration, especially the rapid IV injection of ranitidine, may cause nausea, vomiting, or bradycardia. There is concern that severely ill or stressed animals may require larger than currently recommended doses in order to suppress gastric acid secretion; this is being investigated.

Proton pump inhibitors (i.e., Omeprazole [Prilosec], lansoprazole [Prevacid], and pantoprazole [Protonix]) block the final common pathway of gastric acid secretion. This is the most effective class of drugs for decreasing gastric acid secretion, but maximum suppression of acid secretion takes between 2 and 5 days when administered orally. Omeprazole is a noncompetitive inhibitor primarily used in animals with severe gastroesophageal reflux or gastrinomas (diseases in which H<sub>2</sub> receptor-antagonists are often inadequate). It is uncertain whether most animals with gastric ulcers benefit from the enhanced blockade of gastric acid secretion that this drug provides, as compared with H<sub>2</sub> receptor-antagonist therapy.

## INTESTINAL PROTECTANTS

Intestinal protectants (Table 30-5) include drugs and inert adsorbents such as kaolin, pectin and barium sulfate contrast media. Many people believe that inert adsorbents hasten clinical relief in animals with minor inflammation, possibly because they coat the mucosa or adsorb toxins. They probably make fecal consistency more normal simply by increasing fecal particulate matter. Inert adsorbents do not have a proven efficacy in the treatment of gastritis or enteritis. It is inappropriate to rely on these drugs alone in very sick animals.

Sucralfate (Carafate) is principally indicated for animals with gastroduodenal ulceration or erosion but might also be useful for those with esophagitis (especially if administered as a slurry). It does not appear to effectively prevent NSAID-induced ulceration but may help prevent stress ulceration. Sucralfate is a nonabsorbable, sulfated sucrose complex that protects denuded mucosa by adhering tightly to it. It also inhibits peptic activity and may alter prostaglandin synthesis and the actions of endogenous sulfhydryl compounds. The dose is extrapolated from humans on the basis of the animal's weight. Although no supportive data are available for dogs and cats, sucralfate and H<sub>2</sub> receptor-antagonists are often used concurrently in animals with severe gastrointes-

PO, Orally; SC, subcutaneously; IM, intramuscularly; IV, intravenously.

<sup>\*</sup> Dosages are for both dags and cats unless otherwise specified. † Dosages based upon anecdotal reports. These drugs have not been used extensively, and their saftey and efficacy in dogs are not established.

<sup>§</sup> Anecdotal reports suggest that higher doses may be necessary in severely ill or severely stressed patients.



# TABLE 30-5

# Selected Gastrointestinal Protectants and Cytoprotective Agents

DRUG	DOSAGE*	COMMENT
Sucralfate (Carafate)	0.5-1 g (dogs) or 0.25 g (cats) PO q6-8h, depending on animal's size	Potentially constipating, absorbs some other orally administered drugs, primarily used to treat existing ulcers
Misoprostol (Cytotec)	2-5 μg/kg PO q8h (dogs)	May cause diarrhea/abdominal cramps, primarily used to prevent ulcers, not for use in pregnant animals

<sup>\*</sup> Dosages are for both dogs and cats unless otherwise specified.

tinal tract ulceration or erosion. However, because sucralfate may adsorb other drugs, other orally administered drugs should probably be given 1 to 2 hours before or after sucralfate administration. An acidic pH promotes optimal activity, and there is typically sufficient acid remaining after  $H_2$  receptor—antagonist therapy for sucralfate to be effective. There are no absolute contraindications to the use of sucralfate. The biggest disadvantage is that it must be given orally, and many animals that need it are vomiting. Sucralfate can cause constipation.

Misoprostol (Cytotec) is a prostaglandin E<sub>1</sub> analog used to treat ulcers but especially to help prevent NSAID-induced gastroduodenal ulceration. The drug is primarily used in dogs that require NSAIDs but in which NSAIDs cause anorexia or vomiting. Use of NSAIDs that have a higher risk of causing gastrointestinal tract problems (e.g., piroxicam) might also be an indication. Misoprostol does not appear to be as effective in preventing NSAID-induced ulcers in dogs as it is in people. The major adverse effects of misoprostol seem to be abdominal cramping and diarrhea, which usually disappear after 2 to 3 days of therapy. Pregnancy may be a contraindication. There is evidence that misoprostol may have immunosuppressant properties, especially in combination with other drugs.

## DIGESTIVE ENZYME SUPPLEMENTATION

Pancreatic enzyme supplementation is indicated to treat exocrine pancreatic insufficiency; however, it is often used empirically without justification in animals with diarrhea. There are many products that vary greatly in their potency. Although pills may work, powdered preparations tend to be more effective; enteric-coated pills are particularly ineffective. Viokase-V (A.H. Robins Co.) and Pancreazyme (Daniels Pharmaceuticals) seem to be particularly efficacious. The powder should be mixed with the food (approximately 1 to 2 teaspoons per meal), but allowing the mixture to "incubate" before feeding has not been found beneficial. Fat is the main nutrient that must be digested in animals with exocrine pancreatic insufficiency, and feeding them a low-fat diet may ameliorate diarrhea. Antacid or antibiotic therapy (or both) may occasionally help prevent gastric acidity or small intes-



# TABLE 30-6

Selected Drugs Used to Treat Diarrhea Symptomatically

0	, 1			
DRUG	DOSAGE*			
Intestinal Motility Modifiers				
Anticholinergic drugs				
Methscopolamine (Pamine)	0.3-1.0 mg/kg PO q8h (dog)			
Propantheline (Pro- Banthine)	0.25-0.5 mg/kg PO q8-12h			
Opiates				
Diphenoxylate (Lomotil)	0.05-0.2 mg/kg PO q8-12h (dogs)			
Loperamide	0.1-0.2 mg/kg PO q8-12h (dogs)			
(Imodium)	0.08-0.16 mg/kg PO q12h (cats)			
Paregoric	0.05 mg/kg PO q12h (dogs)			
Antiinflammatory/Antisecretory Drug				
Bismuth subsalicylate† (Pepto-Bismol, Kaopectate)	1 ml/kg/day PO divided q8-12h (dogs) for 1-2 days			

PO. Orally

tinal bacteria from rendering the enzyme supplementation ineffective. Occasionally, a stomatitis or diarrhea develops in dogs receiving large amounts of enzyme supplementation.

#### **MOTILITY MODIFIERS**

Drugs that prolong the intestinal transit time are principally used to symptomatically treat diarrhea. Although infrequently needed, they are indicated if the diarrhea causes excessive fluid or electrolyte losses or owners demand control of the diarrhea at home. Opiates (Table 30-6) increase resistance to flow by augmenting segmental contraction. They tend to be more effective than parasympatholytics, which paralyze motility in the intestines (i.e., create ileus). Both

<sup>\*</sup> Dosages are for both dogs and cats unless otherwise specified. †This drug contains salicylate and can be nephrotoxic if combined with other nephrotoxic drugs.

classes of drugs have antisecretory effects. Because cats do not tolerate narcotics as well as dogs, opiates should not be used in this species, although loperamide may be used carefully.

Loperamide (Imodium) is available as an over-thecounter drug. Use of loperamide theoretically increases the risk for bacterial proliferation in the intestinal lumen, thus potentially initiating or perpetuating disease; however, this is very rare in clinical practice. An overdose can cause narcotic intoxication (i.e., collapse, vomiting, ataxia, hypersalivation), which requires treatment with narcotic antagonists.

Diphenoxylate (Lomotil) is similar to loperamide but tends to be somewhat less effective. It has more potential for toxicity than loperamide. Rarely, a dog responds to it but not to loperamide. This drug should not be used in cats.

Drugs that shorten the transit time (prokinetic drugs) empty the stomach or increase intestinal peristalsis or both. Metoclopramide is a prokinetic drug that is effective only in the stomach and the proximal duodenum. However, it can be administered parenterally. Adverse effects are mentioned under the section on antiemetics. Cisapride stimulates normal motility from the lower esophageal sphincter to the anus. It is usually effective unless the tissue has been irreparably damaged (e.g., megacolon in cats). Primarily used for the treatment of constipation, it may also be used for the management of gastroparesis (in which it is usually more effective than metoclopramide) and small intestinal ileus. It has rarely been reported to be beneficial in dogs with megaesophagus. Cisapride is no longer available from human pharmacies but is generally available from veterinary pharmacies. It is available only as an oral preparation. It has few significant adverse effects, although intoxication with large doses may cause diarrhea, muscular tremors, ataxia, fever, aggression, and other central nervous system signs. Erythromycin stimulates motilin receptors and enhances gastric motility at doses less than required for antibacterial activity (i.e., 2 mg/kg). It may also increase intestinal motility. Nizatidine and ranitidine are H2 receptor antagonists that also have gastric prokinetic effects at routinely used doses. Bethanechol (Urecholine) is an acetylcholine analog that stimulates intestinal motility and secretion. It produces strong contractions that can cause pain or injure the animal; hence, it is infrequently used, except for increasing urinary bladder contractions. Obstruction of an outflow area can be a contraindication to the use of prokinetic drugs because vigorous contractions against such a lesion may cause pain or perforation. Obstruction of the urinary outflow tract is also a contraindication to the use of bethanechol. Tegaserod (Zelnorm) has prokinetic activity in the canine colon (0.05 to 0.1 mg/kg, q12h), but there is too little information regarding its effectiveness in clinical disease to make recommendations about its use.

Pyridostigmine (Mestinon) inhibits acetylcholinesterase and is used to treat myasthenia gravis (see Chapter 71). It is used for the treatment of acquired megaesophagus associated with the formation of antibodies to acetylcholine recep-

tors. It must be used cautiously because overdose may cause toxicity accompanied by signs of parasympathetic overload (e.g., vomiting, miosis, diarrhea). Azathioprine (with or without steroids) may be a better long-term treatment for myasthenia gravis than pyridostigmine.

# ANTIINFLAMMATORY AND ANTISECRETORY DRUGS

Intestinal antiinflammatory or antisecretory drugs (or both) are indicated for lessening the fluid losses resulting from diarrhea or for controlling intestinal inflammation that is unresponsive to dietary or antibacterial therapy.

Bismuth subsalicylate (Pepto-Bismol, Kaopectate) is an over-the-counter antidiarrheal agent that is effective in many dogs with acute enteritis (see Table 30-6), probably because of the antiprostaglandin activity of the salicylate moiety. The main disadvantages are that the salicylate is absorbed (warranting its cautious use in cats or in dogs receiving other nephrotoxic drugs), it turns stools black (which mimics melena), and it must be administered orally (many animals dislike its taste). Bismuth is bactericidal for certain organisms (e.g., *Helicobacter* spp.).

Octreotide (Sandostatin) is a synthetic analog of somatostatin that inhibits alimentary tract motility and the secretion of gastrointestinal hormones and fluids. It has had limited use in dogs and cats but might be helpful in a few animals with intractable diarrhea or pancreatitis.

Salicylazosulfapyridine (sulfasalazine [Azulfidine]) is indicated for animals with colonic inflammation. This drug is generally not beneficial in animals with small intestinal problems. It is a combination of sulfapyridine and 5-aminosalicylic acid. Colonic bacteria split the molecule, and the 5-aminosalicylic acid (probably the active moiety) is subsequently deposited on diseased colonic mucosa. Dogs generally receive 50 to 60 mg/kg, divided into three doses daily, but not to exceed 3 g daily. Sulfasalazine may be effective at lower-than-expected doses if used in combination with glucocorticoids. Empirically, 15 mg/kg/day, sometimes divided into twice-daily doses, is often tolerated by cats, but they must be closely observed for the development of salicylate intoxication (i.e., lethargy, anorexia, vomiting, hyperthermia, tachypnea). Some cats that vomit or become anorectic may tolerate the medication if it is given in entericcoated tablets. Many dogs with colitis respond to therapy in 3 to 5 days. However, the drug should be given for 2 weeks before deciding that it is ineffective. If signs of colitis resolve, the dose of the drug should be gradually reduced. If the animal cannot be weaned off the drug entirely, the lowest effective dose should be used and the animal monitored regularly for the development of drug-induced adverse effects (especially those resulting from the sulfa drug). Sulfasalazine may cause transient or permanent keratoconjunctivitis sicca. Other possible complications include cutaneous vasculitis, arthritis, bone marrow suppression, diarrhea, and any other problem associated with sulfa drugs or NSAIDs.

Olsalazine and mesalamine contain or are metabolized to 5-aminosalicylic acid but do not have the sulfa, which is responsible for most of sulfasalazine's adverse effects. In people they are as effective as sulfasalazine but safer. Olsalazine and mesalamine have been used effectively in dogs. They are given in a dose generally about one half that of sulfasalazine. Keratoconjunctivitis sicca has also been found in dogs receiving mesalamine.

Corticosteroids are specifically indicated in animals with chronic alimentary tract inflammation (e.g., moderate to marked inflammatory bowel diseases) that is not responsive to well-designed elimination diets. In cats prednisolone appears to have better activity than prednisone. Relatively high doses (i.e., prednisolone, 2.2 mg/kg/day) are often used initially, and the dose is tapered to find the lowest effective dose. Dexamethasone is sometimes effective when prednisolone is not, but dexamethasone has more adverse effects than prednisolone. If PO administration is a problem in a cat, long-lasting steroid injections (e.g., methylprednisolone acetate) may be tried.

Methyprednisolone appears to be more effective than prednisolone, requiring only 80% of the dose used for prednisolone. Budesonide (Entocort) is a steroid that is not more effective than prednisolone but is largely eliminated by first pass metabolism in the liver, which decreases its systemic effects. The response may be rapid or take weeks.

Corticosteroids are often beneficial in cats with inflammatory bowel disease, but they may worsen intestinal disease in some dogs and cats. Iatrogenic Cushing's syndrome is more of a problem in dogs but can occur in cats that are grossly overdosed. It is important to have a histologically based diagnosis before using high-dose prednisolone therapy because some diseases that mimic steroid-responsive lymphocytic colitis (e.g., histoplasmosis) are absolute contraindications to corticosteroid therapy. Although more common in the southeastern United States and the Ohio River Valley, histoplasmosis has been found in unexpected states.

Retention enemas of corticosteroids or 5-aminosalicylic acid are sometimes indicated in animals with severe distal colitis. The dose is estimated from the human dose. These enemas place large doses of an antiinflammatory agent directly on the affected area while minimizing systemic effects. Although effective in controlling the clinical signs, their administration is unpleasant for both clients and animals. Further, the active ingredient may be absorbed if there is substantial inflammation and increased mucosal permeability (i.e., animals receiving corticosteroid enemas can become polyuric and polydipsic). Therapeutic retention enemas are typically used until the clinical signs are controlled and other therapy (e.g., sulfasalazine, diet) becomes effective. The contraindications to their use are the same as those to the systemic administration of the active ingredient of the enema.

Immunosuppressive therapy (e.g., azathioprine, chlorambucil, cyclosporine) is indicated in animals with severe inflammatory bowel disease that is unresponsive to corticosteroid and dietary therapy. It is also used in animals with severe disease in which it is in the animal's best interest to use aggressive therapy initially. These drugs should be used only if the diagnosis has been confirmed histopathologically. Immunosuppressive therapy can be more efficacious than corticosteroid therapy alone and allows corticosteroids to be given at lower doses and for shorter periods, thereby decreasing their adverse effects. However, the possibility of adverse effects from these drugs usually limits their use to animals with severe disease. The reader is referred to Chapter 103 for additional information on immunosuppressive therapy.

Azathioprine (Imuran) is commonly used in dogs (50 mg/m² daily or every other day) with severe alimentary tract inflammation. Azathioprine should not be used in cats because of the risk for myelotoxicity. For smaller dogs a 50-mg azathioprine tablet is typically crushed and suspended in a liquid (e.g., 15 ml of a vitamin supplement) to allow more accurate dosing. The suspension must be mixed well before each dosing. It may take 2 to 5 weeks before the beneficial effects of this drug are seen. Side effects in dogs may include hepatic disease, pancreatitis, and bone marrow suppression.

Chlorambucil is an alkylating agent that is used for the same reasons as azathioprine. Chlorambucil, however, appears to have fewer adverse effects than azathioprine. A reasonable starting dose in cats is 1 mg twice weekly for cats weighing less than 7 lb (3.5 kg) and 2 mg twice weekly for cats weighing more than that. Beneficial effects may not be seen for 4 to 5 weeks. If a response is seen, the dose should then be decreased very slowly over the next 2 to 3 months. The animal should be monitored for myelosuppression. Stronger alkylating agents, such as cyclophosphamide, are seldom used for the management of nonneoplastic gastrointestinal tract disease.

Cyclosporine (Atopica) is a potent immunosuppressive drug that is sometimes used in dogs with inflammatory bowel disease, lymphangiectasia, and perianal fistulas. The dose is 3 to 5 mg/kg q12h when given orally, but erratic bioavailability requires therapeutic drug monitoring and subsequent adjusting of the dose. There is considerable variation in the bioavailability of different preparations of cyclosporine. It may be administered intravenously in vomiting patients, but then the initial dose should probably be decreased by 50%. Because of its considerable expense, it is sometimes administered with low doses of ketoconazole (3 to 5 mg/kg q12h), which inhibits metabolism of cyclosporine and in turn allows the use of lower doses at less expense to the client.

# **ANTIBACTERIAL DRUGS**

In dogs and cats with gastrointestinal problems, antibiotics are primarily indicated if aspiration pneumonia, fever, a leukogram suggestive of sepsis, severe neutropenia, antibiotic-responsive enteropathy, clostridial colitis, symptomatic Helicobacter gastritis, or perhaps hematemesis or melena is found or suspected. Animals with an acute abdomen may reasonably be treated with antibiotics while the nature of the disease is being defined. Acute colitis is a reasonable indication for amoxicillin (22 mg/kg q12h) because clostridial colitis is reasonably common. However, most animals with acute enteritis or gastritis of unknown cause do not benefit from antibiotic therapy. In general, the routine use of antimicrobials in animals with alimentary tract disorders is not recommended, unless the animal is at high risk for infection or a specific disorder is being treated.

Nonabsorbable aminoglycosides (e.g., neomycin) are often used to "sterilize" the intestines. However, they do not kill anaerobic bacteria, which are the predominant type found there. Further, there are a plethora of viral and dietary causes of acute enteritis that are not responsive to antibiotics. Thus aminoglycosides given orally are not indicated unless a specific infection (e.g., campylobacteriosis) is being considered.

Broad-spectrum antibiotics effective against aerobes and anaerobes may be used for the treatment of antibioticresponsive enteropathy (ARE). Metronidazole (10 to 15 mg/ kg q24h) may also be used for this purpose (see later discussion) but has not been as successful in this author's experience. Tylosin (20 to 40 mg/kg q12h) is commonly used for this purpose. Tetracycline (22 mg/kg q12h) has also been used, and patients with severe disease believed to have ARE may be treated with combinations (e.g., metronidazole and enrofloxacin [7 mg/kg .q24h]). Inappropriate antibiotic therapy may hypothetically eliminate enough resident bacteria that overgrowth of pathogenic bacteria in the colon occurs. However, this is rarely a clinical problem in dogs and cats. The clinician should treat the patient for at least 2 to 3 weeks before deciding that therapy for ARE has been unsuccessful.

Pets occasionally have enteritis caused by a specific bacterium. However, even this is not necessarily an indication for antibiotics. Clinical signs resulting from some bacterial enteritides (e.g., salmonellosis, enterohemorrhagic *Escherichia coli*) generally do not resolve more quickly when the animal is treated with antibiotics, even those to which the bacteria are sensitive.

Dogs and cats with viral enteritis but without obvious systemic sepsis may reasonably be treated with antibiotics if secondary sepsis is likely to occur (e.g., those with neutropenia or severe hemorrhagic diarrhea). First-generation cephalosporins (e.g., cefazolin) are often effective for such use.

If systemic or abdominal sepsis is suspected to have originated from the alimentary tract (e.g., septicemia caused by parvoviral enteritis, perforated intestine), broad-spectrum antimicrobial therapy is indicated. Antibiotics with a good aerobic gram-positive and anaerobic spectrum of action (e.g., ticarcillin plus clavulinic acid [Timentin], 50 mg/kg given intravenously three to four times daily, or clindamycin, 11 mg/kg given intravenously three times daily) combined with antibiotics with excellent activity against most aerobic

bacteria (e.g., amikacin, 25 mg/kg given intravenously once daily or enrofloxacin, 15 mg/kg given intravenously once daily) are often effective. To improve the anaerobic spectrum, especially if a cephalosporin is used instead of ampicillin, the clinician may include metronidazole (10 mg/kg given intravenously two or three times daily). Alternatively, a second-generation cephalosporin (e.g., cefoxitin, 30 mg/kg given intravenously three or four times daily) may be used. In general, it takes at least 48 to 72 hours before the clinician can tell whether the therapy will be effective.

Helicobacter gastritis may be treated with various combinations of drugs. Currently, the combination of an antacid (i.e., famotidine or omeprazole; see Table 30-4) and a macrolide (i.e., erythromycin or azithromycin; see pp. 483–485) or amoxicillin seems to be very effective. Adding metronidazole and/or bismuth subsalicylate may enhance efficacy. However, some patients seem to respond to erythromycin or amoxicillin as a sole agent. If high doses of erythromycin (22 mg/kg given twice daily) cause vomiting, the dose may be lowered to 10 to 15 mg/kg given twice daily. A 10- to 14-day course of treatment appears to be adequate for most animals, although recurrence of infection is possible.

Metronidazole is a "miscellaneous" drug that is commonly used in animals with inflammatory bowel disease. It has antimicrobial activity against anaerobic bacteria (which predominate in the gastrointestinal tract) and protozoa (e.g., Giardia). It has been suggested to have some effect on the immune system, as shown by its apparent beneficial effects in people with Crohn's disease. The usefulness of metronidazole in dogs and cats with inflammatory bowel disease (10 to 15 mg/kg given twice daily) is suspected but unproved. Adverse effects are uncommon but may include salivation (because of its taste), vomiting, central nervous system abnormalities (e.g., central vestibular signs), and perhaps neutropenia. These adverse effects usually resolve after withdrawing the drug. Cats sometimes accept oral suspensions better than the 250-mg tablets, which must be cut and have an unpleasant taste. Some cats diagnosed with inflammatory bowel disease respond to metronidazole better than they do to corticosteroids. Occasionally, dogs with colitis do likewise.

### PROBIOTICS/PREBIOTICS

The administration of live bacteria or yeast in the food with the intent to produce a beneficial effect is called *probiotic therapy*. The administration of a specific dietary substance to specifically increase or decrease the numbers of specific bacteria is called *prebiotic therapy*. The concurrent use of probiotics and prebiotics is called *symbiotic therapy*. Although there is good evidence that these therapies are beneficial for specific conditions in people, there is currently no published work showing a clear benefit in clinically ill dogs or cats. However, this may change with time.

Lactobacillus, Bifidobacterium, and Enterococcus are the bacteria typically administered to dogs. These bacteria are

believed to stimulate Toll-like receptors in the bowel and thereby benefit the patient. The beneficial effect seems to last only as long as the bacteria are being administered. There is no evidence that these bacteria become permanently established in the gastrointestinal microflora during administration. Not all probiotics sold in drug or grocery stores contain what the label states, which may be at least partially responsible for their failure to have demonstrated efficacy. In general, large numbers of bacteria appear to be necessary, which explains why feeding yogurt (which contains relatively modest numbers of *Lactobacilli*) is ineffective. At the time of this writing, there are two products marketed specifically for veterinary use (Fortiflora, Purina Co) that contains *Enterococcus faecium* and Proviable (Nutramax) that contains a mixture of several bacteria.

# **ANTHELMINTIC DRUGS**

Anthelmintics are frequently prescribed for dogs and cats with alimentary tract disease, even if parasitism is not the primary problem. It is often reasonable to use these drugs empirically for the treatment of suspected parasitic infections in animals with acute or chronic diarrhea. Selected anthelmintics are listed in Table 30-7.

# **ENEMAS, LAXATIVES, AND CATHARTICS**

Enemas are classified as either cleansing or retention.

Retention enemas are given so that the material administered stays in the colon until it exerts its desired effects (e.g., antiinflammatory retention enemas are used in animals with inflammatory bowel disease, water in obstipated animals). Obstipated animals may require frequent administrations of modest volumes of water (e.g., 20 to 200 ml, depending on the animal's size) so that the water stays in the colon and gradually softens the feces. The clinician should avoid overdistending the colon or administering drugs that may be absorbed and produce undesirable effects. Suspected or pending colonic rupture is a contraindication to the use of enemas, but this outcome is difficult to predict. Animals that have undergone neurosurgery (e.g., those that have had a hemilaminectomy) and are receiving corticosteroids (e.g., dexamethasone) may be at increased risk for colonic perforation. Animals with colonic tumors or that have recently undergone colonic surgery or biopsy should not receive enemas either, unless there is an overriding reason.

Cleansing enemas are designed to remove fecal material. They involve the repeated administration of relatively large volumes of warm water. In dogs the water is administered by gravity flow from a bucket or bag held above the animal. The tube is gently advanced as far as it will easily go into the colon. Between 50 and 100 ml is tolerated by most small dogs, 200 to 500 ml by medium-size dogs, and 1 to 2 L by large dogs. Care should be taken to avoid overdistending or

perforating the colon. Enemas are usually administered to cats with a soft canine male urinary catheter and a 50-ml syringe. If fluid is administered too quickly, however, the cat will usually vomit. A suspected or pending colonic perforation is also a contraindication to a cleansing enema.

Hypertonic enemas are potentially dangerous and should be used cautiously (if at all) because they can cause massive, fatal fluid and electrolyte shifts (i.e., hyperphosphatemia, hypocalcemia, hypokalemia, hyperkalemia). This is especially true for cats, small dogs, and any animal that cannot quickly evacuate the enema because of obstipation.

Cathartics and laxatives (Table 30-8) should be used only to augment defecation in animals that are not obstructed. They are not routinely indicated in small animals, except perhaps as part of lower bowel cleansing before contrastenhanced abdominal radiography or endoscopy.

Irritative laxatives (e.g., bisacodyl) stimulate defecation rather than soften feces. They are often used before colonoscopic procedures and in animals that are reluctant to defecate because of an altered environment. They are probably not appropriate for long-term use because of the dependence and colonic problems noted in people who have used them inappropriately. A glycerin suppository or a lubricated match stick is often an effective substitute for an irritative laxative. These objects are carefully placed in the rectum to stimulate defecation.

Bulk and osmotic laxatives include a variety of preparations: various fibers (especially the soluble ones); magnesium sulfate; lactulose; and, in milk-intolerant animals, ice cream or milk. They promote the fecal retention of water and are indicated in animals that have overly hard stools not caused by the ingestion of foreign objects. These laxatives are more appropriate for long-term use than the irritative cathartics are. Larger doses may be needed in cats because they retain fluids more effectively than dogs do.

Fiber is a bulking agent that is incorporated into the food and can be used indefinitely. Commercial diets relatively high in fiber may be used, or existing diets may be supplemented with fiber (see pp. 400–401). It is important to supply adequate amounts of water so that the additional fiber does not cause the formation of harder-than-normal stools. Too much fiber may cause excessive stool or inappetence resulting from decreased palatability (a danger for fat cats at risk for hepatic lipidosis). Fiber should not be given to animals with a partial or complete alimentary tract obstruction because impaction may occur.

Lactulose (Cephulac) was designed to control signs of hepatic encephalopathy, but it is also a very effective osmotic laxative. It is a disaccharide that is split by colonic bacteria into unabsorbed particles. Lactulose is particularly useful for animals that refuse to eat high-fiber diets. The dose necessary to soften feces must be determined in each animal, but 0.5 or 5 ml may be given two or three times daily to small and large dogs, respectively. Cats often need higher dosages (e.g., 5 ml three times daily). If gross overdosing occurs, so much water can be lost that hypernatremic dehydration ensues. There are no obvious contraindications to the use of lactulose.



DRUG	DOSAGE* (PO)	USE	COMMENTS
Albendazole (Valbazen)	25 mg/kg q12h for 3 days (dogs only) 25 mg/kg q12h for 5 days (cats only)	G	May cause leukopenia in some animals. Do not use in early pregnancy. Not approved for use in dogs.
Fenbendazole (Panacur)	50 mg/kg for 3-5 days	H/R/W/G	Not approved for cats but often used for 3-5 days in cats to eliminate Giardia. Give with food.
Furazolidone Metronidazole (Flagyl)	4.4 mg/kg q12h for 5 days 25-50 mg/kg for 5-17 days (dogs only) 25-50 mg/kg for 5 days (cats only)	G G	— Rarely see neurologic signs.
Ronidazole	30-50 mg/kg q12h for 14 days (cats only)		For <i>Tritrichomonas</i> infections in cats; drug is not approved for use in animals. Rarely causes neurologic signs.
Pyrantel (Nemex)	5 mg/kg (dogs only) 20 mg/kg, once only (cats only)	H/R/P	Give after meal
Pyrantel/febantel/ praziquantel (Drontal Plus)	1 tablet/10 kg	T/H/R/W	
Imidocloprid/moxidectin (Advantage multi)	Topical—Follow manufacturers' recommendations	H/R/W	
lvermectin	200 μg/kg (dogs only)	H/R/P	Do not use in Collies, Shelties, Border Collies, or Australian Shepherds. Use with caution in Old English Sheepdogs. Only approved for use as heartworm preventive.  Safe to use in dogs with <i>D immitis</i> microfilaremia. Treats <i>Strongyloides</i> .  Generally should use only if other drugs not appropriate.
Milbemycin (Interceptor)	0.5 mg/kg, monthly	H/R/W	Not approved for use in cats. Not safe to use in dogs with <i>D. immitis</i> microfilaremia.
Praziquantel (Droncit)	5 mg/kg for dogs >6.8 kg	Т	10 mg/kg for juvenile Echinococcus
	7.5 mg/kg for dogs <6.8 kg 6.3 mg/kg for cats <1.8 kg 5 mg/kg for cats >1.8 kg For <i>Heterobilharzia</i> , 20 mg/kg SC q8h for 1 day (dog only)		spp.
Episprantel (Cestex)	5.5 mg/kg for dogs 2.75 mg/kg for cats	T	_
Selamectin (Revolution) Sulfadimethoxine (Albon)	6 mg/kg topical for cats 50 mg/kg on day 1, then 27.5 mg/kg q12h for 9 days	H/R C	Not approved for use in dogs.  May cause dry eyes, arthritis,  cytopenia, hepatic disease.
Trimethoprim-sulfadiazine (Tribrissen)	30 mg/kg for 10 days	С	May cause dry eyes, arthritis, cytopenia, hepatic disease.

PO, orally; G, Giardia; H, hookworms; R, roundworms; W, whipworms; P, Physaloptera; T, tapeworms; C, coccidia. \*Dosages are for both dogs and cats unless otherwise specified.



# Selected Laxatives, Cathartics, Stool-Softening Agents, and Bulking Agents

DOSAGE (PO)	COMMENTS
5 mg (small dogs and cats) 10-15 mg (larger dogs)	Do not break tablets
1-3 tbsp/454 g of food	
I-3 tbsp/day (cats only)	Principally for cats
10-200 mg q8-12h (dogs only) 10-25 mg q12-24h (cats only)	Be sure animal is not dehydrated when treating
1 ml/5 kg q8-12h, then adjust dose as needed (dogs only)	Can cause severe osmotic diarrhea
5 ml q8h, then adjust dose as needed	
1-2 tsp/454 g of food	Be sure animal has enough water, or constipation may develop
	5 mg (small dogs and cats) 10-15 mg (larger dogs) 1-3 tbsp/454 g of food 1-3 tbsp/day (cats only) 10-200 mg q8-12h (dogs only) 10-25 mg q12-24h (cats only) 1 ml/5 kg q8-12h, then adjust dose as needed (dogs only) 5 ml q8h, then adjust dose as needed (cats only)

PO, Orally.

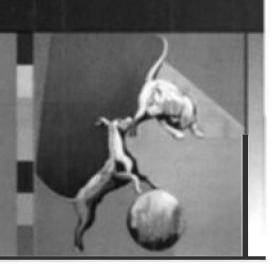
# Suggested Readings

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# CHAPTER

# Disorders of the Oral Cavity, Pharynx, and Esophagus



# CHAPTER OUTLINE

# MASSES, PROLIFERATIONS, AND INFLAMMATION OF THE OROPHARYNX

Sialocele

Sialoadenitis/Sialoadenosis/Salivary Gland Necrosis

Neoplasms of the Oral Cavity in Dogs

Neoplasms of the Oral Cavity in Cats

Feline Eosinophilic Granuloma

Gingivitis/Periodontitis

**Stomatitis** 

Feline Lymphocytic-Plasmacytic Gingivitis/Pharyngitis DYSPHAGIAS

Masticatory Muscle Myositis/Atrophic Myositis

Cricopharyngeal Achalasia/Dysfunction

Pharyngeal Dysphagia

# ESOPHAGEAL WEAKNESS/MEGAESOPHAGUS

Congenital Esophageal Weakness

Acquired Esophageal Weakness

Esophagitis

Hiatal Hernia

Dysautonomia

## **ESOPHAGEAL OBSTRUCTION**

Vascular Ring Anomalies

Esophageal Foreign Objects

Esophageal Cicatrix

Esophageal Neoplasms

# MASSES, PROLIFERATIONS, AND INFLAMMATION OF THE OROPHARYNX

# **SIALOCELE**

# **Etiology**

Sialoceles are accumulations of saliva in subcutaneous tissues caused by salivary duct obstruction and/or rupture and subsequent leakage of secretions into subcutaneous tissues. Most cases are probably traumatic, but some are idiopathic.

#### **Clinical Features**

A large, usually painless swelling is found under the jaw or tongue or occasionally in the pharynx. Oral cavity sialoceles may cause dysphagia, whereas those located in the pharynx often produce gagging or dyspnea. If traumatized, sialoceles may bleed or cause anorexia due to discomfort.

# Diagnosis

Aspiration with a large-bore needle reveals thick fluid with some neutrophils. The fluid usually resembles mucus, strongly suggesting its salivary gland origin. Contrast radiographic procedures (contrast sialograms) sometimes define which gland is involved.

#### **Treatment**

The mass is opened and drained, and the salivary gland responsible for the secretions must be excised.

## **Prognosis**

The prognosis is excellent if the correct gland is removed.

# SIALOADENITIS/SIALOADENOSIS/ SALIVARY GLAND NECROSIS

#### Etiology

The etiology is unknown, but the condition apparently has occurred as an idiopathic event as well as secondary to vomiting/regurgitation.

#### **Clinical Features**

The condition may cause a painless enlargement of one or more salivary glands (usually the submandibular). If there is substantial inflammation, animals may be dysphagic. A syndrome has been reported in which noninflammatory swelling is associated with vomiting that is responsive to phenobarbital therapy. This syndrome has no established cause and effect.

## **Diagnosis**

Biopsy and cytology or histopathology confirm that the mass is salivary tissue and determine whether inflammation or necrosis is present.

#### **Treatment**

If there is substantial inflammation and pain, surgical removal seems most efficacious. If the patient is vomiting, a search should be made for an underlying cause. If a cause is found, it should be treated and the size of the salivary glands monitored. If no other cause for vomiting can be found, phenobarbital may be administered at anticonvulsant doses (see Chapter 67).

# **Prognosis**

The prognosis is usually excellent.

# NEOPLASMS OF THE ORAL CAVITY IN DOGS

### Etiology

Most soft tissue masses of the oral cavity are neoplasms, and most of these are malignant (i.e., melanoma, squamous cell carcinoma, fibrosarcoma). However, acanthomatous ameloblastomas (previously called *epulides*), fibromatous epulides

(classically in Boxers), oral papillomatosis, and eosinophilic granulomas (e.g., in Siberian Huskies and Cavalier King Charles Spaniels) also occur.

#### **Clinical Features**

The most common signs of tumors of the oral cavity are halitosis, dysphagia, bleeding, or a growth protruding from the mouth. Papillomatosis and fibromatous periodontal hyperplasia are benign growths that may cause discomfort when eating and occasionally cause bleeding, mild halitosis, or tissue protrusion from the mouth. The biologic behaviors of the different tumors are presented in Table 31-1.

## Diagnosis

A thorough examination of the oral cavity (which may require that the animal be under anesthesia) usually reveals a mass involving the gingiva, although the tonsillar area, hard palate, and tongue can also be affected. Diagnosis requires cytologic or histopathologic analysis, although papillomatosis and melanomas may be strongly suspected on the basis of their



**TABLE 31-1** 

Some Characteristics of Selected Oral Tumors

TUMOR	TYPICAL APPEARANCE/ LOCATION	BIOLOGIC BEHAVIOR	PREFERRED THERAPY
Squamous Cell Carc	inoma		
Gingiva	Fleshy or ulcerated/on rostral gingiva	Malignant, locally invasive	Wide surgical resection on rostral gingiva ± radiation; piroxicam often helpful
Tonsil	Fleshy or ulcerated/on one or rarely both tonsils	Malignant, commonly spreads to regional lymph nodes	None (chemotherapy may be of some benefit); piroxicam may be helpful
Tongue margin (dog)	Ulcerated/on margin of tongue	Malignant, locally invasive	Surgical resection of tongue/radiotherapy; piroxicam may be helpful
Base of tongue (cat)	Ulcerated/at base of tangue	Malignant, locally invasive	None (radiotherapy of tongue and/or chemotherapy may be used palliatively)
Malignant Melanoma	Grey or black; can be smooth, usually fleshy/ on gum, tongue, or palate	Very malignant, early metastases to lungs	None (resection and/or radiation are palliative but rarely curative); carboplatin and radiation might help. A vaccine recently has been released; initial reports are encouraging.
Fibrosarcoma	Pink and fleshy/on palate or gums	Malignant, very invasive locally	Wide surgical resection (chemotherapy and/or radiation may be of some value in selected cases)
Acanthomatous Ameloblastoma (Epulis)	Pink and fleshy/on gum or rostral mandible	Malignant, locally invasive	Surgical resection ± radiation
Fibromatous Epulis	Pink, fleshy, solitary or multiple/on gums	Benign	Nothing or surgical resection
Papillomatosis	Pink or white, cauliflower- like, multiple/seen anywhere	Benign	Nothing or surgical resection
Plasmacytoma	Fleshy or ulcerated growth on gingiva	Malignant, locally invasive Rarely metastasizes	Surgical resection ± radiation

gross appearance. The preferred diagnostic approach in a dog with a mass of the oral cavity is to perform an incisional biopsy and to obtain thoracic and skull radiographs or a computed tomography (CT) scan of the affected area. If malignancy is a diagnostic consideration, thoracic radiographs should be obtained to evaluate for metastases (seldom seen but a very poor prognostic sign if present), and maxillary and mandibular radiographs should be obtained to check for bony involvement. Fine-needle aspiration of regional lymph nodes, even if they appear normal, is indicated to detect metastases. Melanomas may be amelanotic and can cytologically resemble fibrosarcomas, carcinomas, or undifferentiated round cell tumors. Biopsy and subsequent histopathologic analysis may be required for a definitive diagnosis.

# **Treatment/Prognosis**

The preferred therapeutic approach in dogs with confirmed malignant neoplasms of the oral cavity and lack of clinically detectable metastases is wide, aggressive surgical excision of the mass and surrounding tissues (e.g., mandibulectomy, maxillectomy). Enlarged regional lymph nodes should be excised and evaluated histopathologically, even if they are cytologically negative for neoplasia. Early complete excision of gingival or hard palate squamous cell carcinomas, fibrosarcomas, acanthomatous epulides, and (rarely) melanomas may be curative. Acanthomatous epulis and ameloblastomas may respond to radiation therapy alone (complete surgical excision is preferred), and squamous cell carcinomas or fibrosarcomas with residual postoperative disease may benefit from postoperative adjunctive radiation therapy. Lingual squamous cell carcinomas affecting the base of the tongue and tonsillar carcinomas have a very poor prognosis; complete excision or irradiation usually causes severe morbidity. Melanomas metastasize early and have a very guarded prognosis. Chemotherapy is usually not beneficial in dogs with squamous cell carcinoma, acanthomatous epulis, and melanoma, but an oncologist should be consulted about new protocols that may provide some benefit. Piroxicam can benefit some patients with squamous cell carcinoma. Combination chemotherapy may be beneficial in some dogs with fibrosarcoma (see Chapter 77). Radiotherapy plus hyperthermia has been successful in some dogs with oral fibrosarcoma.

Papillomatosis usually resolves spontaneously, although it may be necessary to resect some of the masses if they interfere with eating. Fibromatous epulides may be resected if they cause problems.

# NEOPLASMS OF THE ORAL CAVITY IN CATS

### Etiology

Tumors of the oral cavity are less common in cats than in dogs, but they are usually squamous cell carcinomas, which are diagnosed and treated as described for dogs. Cats are different from dogs in that they also have sublingual squamous cell carcinomas and eosinophilic granulomas (which mimic carcinoma but have a much better prognosis).

#### **Clinical Features**

Dysphagia, halitosis, anorexia, and/or bleeding are common features of these tumors.

## Diagnosis

A large, deep biopsy specimen is needed because it is crucial to differentiate malignant tumors from eosinophilic granulomas. The superficial aspect of many masses of the oral cavity is ulcerated and necrotic as a result of the proliferation of normal oral bacterial flora, making it difficult to interpret this part of the mass.

#### **Treatment**

Surgical excision is desirable. Radiation therapy and/or chemotherapy may benefit cats with incompletely excised squamous cell carcinomas not involving the tongue or tonsil.

## **Prognosis**

In general, the prognosis for cats with squamous cell carcinomas of the tongue or tonsil is guarded to poor (see Chapter 82).

#### FELINE EOSINOPHILIC GRANULOMA

## Etiology

The cause of feline eosinophilic granuloma is unknown.

### **Clinical Features**

Feline eosinophilic granuloma complex includes indolent ulcer, eosinophilic plaque, and linear granuloma; however, it has not been established that these diseases are related. Indolent ulcers are classically found on the lip or oral mucosa of middle-aged cats. Eosinophilic plaque usually occurs on the skin of the medial thighs and abdomen. Linear granuloma is typically found on the posterior aspect of the rear legs of young cats but may also occur on the tongue, palate, and oral mucosa. Severe oral involvement of an eosinophilic ulcer or plaque typically produces dysphagia, halitosis, and/or anorexia. Cats with eosinophilic granulomas of the mouth may have concurrent cutaneous lesions.

## Diagnosis

An ulcerated mass may be found at the base of the tongue or on the hard palate, the glossopalatine arches, or anywhere else in the mouth. A deep biopsy specimen of the mass is necessary for accurate diagnosis. Peripheral eosinophilia is inconsistently present.

#### **Treatment**

High-dose corticosteroid therapy (oral prednisolone, 2.2 to 4.4 mg/kg/day) often controls these lesions. Sometimes cats are best treated with methylprednisolone acetate injections (20 mg every 2 to 3 weeks as needed) instead of oral prednisolone. Although effective, megestrol acetate may cause diabetes mellitus, mammary tumors, and uterine problems and probably should not be used except under extreme

constraints. Chlorambucil might prove useful in resistant cases.

# **Prognosis**

The prognosis is good, but the lesion can recur.

# GINGIVITIS/PERIODONTITIS

# **Etiology**

Bacterial proliferation and toxin production, usually associated with tartar buildup, destroy normal gingival structures and produce inflammation. Immunosuppression caused by feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and/or feline calicivirus may predispose some cats to this disease.

#### **Clinical Features**

Dogs and cats may be affected. Many are asymptomatic, but halitosis, oral discomfort, refusal to eat, dysphagia, drooling, and tooth loss may occur.

# Diagnosis

Visual examination of the gums reveals hyperemia around the tooth margins. Gingival recession may reveal tooth roots. Accurate diagnosis can be made through probing and oral radiographs. The stage of periodontal disease is defined by radiographs.

#### **Treatment**

Supragingival and subgingival tartar should be removed, and the crowns should be polished. Antimicrobial drugs effective against anaerobic bacteria (e.g., amoxicillin, clindamycin, metronidazole; see Drugs Used in Gastrointestinal Disorders table, pp. 481–483) may be used before and after cleaning teeth. Regular brushing of the teeth and/or oral rinsing with a veterinary chlorhexidine solution formulated for that purpose helps to control the problem.

#### **Prognosis**

The prognosis is good with proper therapy.

#### **STOMATITIS**

#### Etiology

There are many causes of canine and feline stomatitis (Box 31-1). The clinician should always consider the possibility of immunosuppression with secondary stomatitis (e.g., FeLV, FIV, diabetes mellitus, hyperadrenocorticism).

# **Clinical Features**

Most dogs and cats with stomatitis have thick, ropey saliva; severe halitosis; and/or anorexia caused by pain. Some animals are febrile and lose weight.

### Diagnosis

A thorough oral examination usually requires that the animal be under anesthesia. Stomatitis is diagnosed by gross obser-



#### Common Causes of Stomatitis

Renal failure

Trauma

Foreign objects

Chewing or ingesting caustic agents

Chewing on electrical cords

Immune-mediated disease

Pemphigus

Lupus

Upper respiratory viruses (feline viral rhinotracheitis, feline calicivirus)

Infection secondary to immunosuppression (feline leukemia virus, feline immunodeficiency virus)

Tooth root abscesses

Severe periodontitis

Osteomyelitis

Thallium intoxication

vation of the lesions, but an underlying cause should be sought. Biopsy is routinely indicated, as are routine clinical pathology data and radiographs of the mandible and maxilla, including the tooth roots.

#### Treatment

Therapy is both symptomatic (to control signs) and specific (i.e., directed at the underlying cause). Thorough teeth cleaning and aggressive antibacterial therapy (i.e., systemic antibiotics effective against aerobes and anaerobes, cleansing oral rinses with antibacterial solutions such as chlorhexidine) often help. In some animals extracting teeth that are associated with the most severely affected areas may help. Bovine lactoferrin has been reported to ameliorate otherwise resistant lesions in cats.

#### **Prognosis**

The prognosis depends on the underlying cause.

# FELINE LYMPHOCYTIC-PLASMACYTIC GINGIVITIS/PHARYNGITIS

#### Etiology

An idiopathic disorder, feline lymphocytic-plasmacytic gingivitis might be caused by feline calicivirus or any stimulus producing sustained gingival inflammation. Cats appear to have an excessive oral inflammatory response that can produce marked gingival proliferation.

#### **Clinical Features**

Anorexia and/or halitosis are the most common signs. Affected cats grossly have reddened gingiva around the teeth and/or posterior pillars of the pharynx. The gingiva may be obviously proliferative in severe cases and bleed easily. Dental neck lesions often accompany the gingivitis. Teeth chattering is also occasionally seen.

# Diagnosis

Biopsy of affected (especially proliferative) gingiva is needed for diagnosis. Histologic evaluation reveals a lymphocyticplasmacytic infiltration. Serum globulin concentrations may be increased.

#### **Treatment**

There is currently no reliable therapy for this disorder. Proper cleaning and polishing of teeth and antibiotic therapy effective against anaerobic bacteria may help. High-dose corticosteroid therapy (prednisolone, 2.2 mg/kg/day) is often useful. In some severe cases, multiple tooth extractions may alleviate the source of the inflammation. However, extraction of the canine teeth should be delayed. Immunosuppressive drugs such as chlorambucil also may be tried in obstinate cases.

## **Prognosis**

The prognosis is guarded; severely affected animals often do not respond well to therapy.

# DYSPHAGIAS JERPENNICHE MERCHICLE

# MASTICATORY MUSCLE MYOSITIS/ ATROPHIC MYOSITIS

## Etiology

Masticatory muscle myositis/atrophic myositis is an idiopathic, immune-mediated disorder that affects the muscles of mastication in dogs. The syndrome has not been reported in cats.

#### **Clinical Features**

In the acute stages the temporalis and masseter muscles may be swollen and painful. However, many dogs are not presented until the muscles are severely atrophied and the mouth cannot be opened.

## Diagnosis

Atrophy of the temporalis and masseter muscles and the inability to open the dog's mouth while it is anesthetized allow the clinician to establish a presumptive diagnosis. Muscle biopsy of the temporalis and masseter muscles provides confirmation. The presence of antibodies to type 2M fibers strongly supports this diagnosis.

#### **Treatment**

High-dose prednisolone therapy (2.2 mg/kg/day) with or without azathioprine (50 mg/m² q24 h) is usually curative. Once control has been achieved, the prednisolone and azathioprine are administered every 48 hours and then the dose of prednisolone is tapered to avoid adverse effects. However, this tapering must be done slowly to prevent recurrence (see the section on immunosuppressive drugs in Chapter 103). If needed, a gastrostomy tube may be used until the animal can eat.

# **Prognosis**

The prognosis is usually good, but continued medication may be needed.

# CRICOPHARYNGEAL ACHALASIA/ DYSFUNCTION

# Etiology

The cause of cricopharyngeal achalasia/dysfunction is unknown, but it is usually congenital. There is an incoordination between the cricopharyngeus muscle and the rest of the swallowing reflex, which produces obstruction at the cricopharyngeal sphincter during swallowing (i.e., the sphincter does not open at the proper time). The problem has a genetic basis in Golden Retrievers.

#### **Clinical Features**

Primarily seen in young dogs, cricopharyngeal achalasia rarely occurs as an acquired disorder. The major sign is regurgitation immediately after or concurrent with swallowing. Some animals become anorexic, and severe weight loss may occur. Clinically, this condition may be indistinguishable from pharyngeal dysfunction.

## Diagnosis

Definitive diagnosis requires fluoroscopy or cinefluoroscopy while the animal is swallowing barium or another contrast media. A young animal that is regurgitating food immediately on swallowing is suggestive of the disorder, but pharyngeal dysphagia with normal cricopharyngeal sphincter function occasionally occurs as an apparently congenital defect and must be differentiated from cricopharyngeal disease.

## **Treatment**

Cricopharyngeal myotomy can be curative. The clinician must be careful not to cause cicatrix at the surgery site. Esophageal function in the cranial esophagus must be evaluated before this surgery is considered (see the next section, on pharyngeal dysphagia).

# **Prognosis**

The prognosis is good if cicatrix does not occur postoperatively.

### PHARYNGEAL DYSPHAGIA

#### Etiology

Pharyngeal dysphagia is primarily an acquired disorder, and neuropathies, myopathies, and junctionopathies (e.g., localized myasthenia gravis) seem to be the main cause. The inability to form a normal bolus of food at the base of the tongue and/or to propel the bolus into the esophagus is often associated with lesions of cranial nerves IX or X. Simultaneous dysfunction of the cranial esophagus may cause food retention just caudal to the cricopharyngeal sphincter.

### **Clinical Features**

Although pharyngeal dysphagia principally is found in older animals, young animals occasionally have transient signs. Pharyngeal dysphagia often clinically mimics cricopharyngeal achalasia; regurgitation is associated with swallowing. Pharyngeal dysphagia sometimes causes more difficulty with swallowing fluids than solids. Aspiration (especially associated with liquids) is common because the proximal esophagus is often flaccid and retains food, predisposing to later reflux into the pharynx.

## Diagnosis

Fluoroscopy or cinefluoroscopy while the animal is swallowing barium is typically required for diagnosis. An experienced radiologist is needed to reliably distinguish pharyngeal dysphagia from cricopharyngeal dysphagia. With the former condition, the animal does not have adequate strength to properly push boluses of food into the esophagus, whereas in the latter the animal has adequate strength but the cricopharyngeal sphincter stays shut or opens at the wrong time during swallowing, thereby preventing normal movement of food from the pharynx to the proximal esophagus. It appears that some cases may be detected by electromyography of laryngeal, pharyngeal, and esophageal muscles.

#### **Treatment**

Although cricopharyngeal myotomy is often curative for animals with cricopharyngeal achalasia, it may be disastrous for animals with pharyngeal dysphagias because it allows food retained in the proximal esophagus to more easily reenter the pharynx and be aspirated. The clinician must either bypass the pharynx (e.g., gastrostomy tube) or resolve the underlying cause (e.g., treat or control myasthenia gravis).

### **Prognosis**

The prognosis is guarded because it is often difficult to find and treat the underlying cause, and the dog or cat is prone to progressive weight loss and recurring aspiration pneumonia.

# ESOPHAGEAL WEAKNESS/ MEGAESOPHAGUS

## CONGENITAL ESOPHAGEAL WEAKNESS

#### Etiology

The cause of congenital esophageal weakness (i.e., congenital megaesophagus) is unknown. There is no evidence of demyelination or neuronal degeneration, and vagal efferent innervation appears to be normal.

#### **Clinical Features**

Affected animals (primarily dogs) are usually presented because of "vomiting" (actually regurgitation) with or without weight loss, coughing, or fever from pneumonia. Occasionally, coughing and other signs of aspiration tracheitis and/or pneumonia may be the only signs reported by the owner.

## Diagnosis

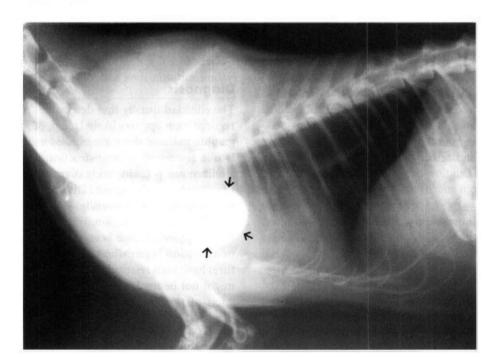
The clinician usually first determines from the history that regurgitation appears likely (see p. 353). Then, after radiographic findings show generalized esophageal dilation that is not associated with obstruction (see Fig. 29-3, A), the clinician can presumptively diagnose esophageal weakness. Diverticula in the cranial thorax caused by esophageal weakness occur occasionally and are often confused with vascular ring obstruction (Fig. 31-1). Congenital, rather than acquired, disease is suspected if the regurgitation and/ or aspiration began when the pet was young. If clinical features have been relatively mild or intermittent, the diagnosis might not be made until the animal is older, but consideration of the history should suggest that signs have been present since the animal was young. Endoscopy is not as useful as contrast radiographs for diagnosing this disorder. Collies may have dermatomyositis, which also causes esophageal weakness. Some breeds (e.g., Miniature Schnauzers, Great Danes, Dalmatians) appear to be at increased

#### **Treatment**

Congenital esophageal weakness currently cannot be cured or resolved by medical therapy, although cisapride (0.25 mg/ kg) seemingly ameliorates signs in rare cases (probably in patients with substantial gastroesophageal reflux). Conservative dietary management is used to try to prevent further dilation and aspiration. Classically, the animal is fed a gruel from an elevated platform that requires the pet to stand on its rear legs. In this manner, the cervical and thoracic esophagus is nearly vertical when food is ingested, which allows gravity to aid food passing through the esophagus and into the stomach. This position should be maintained for 5 to 10 minutes after the animal has finished eating and drinking. If the dog cannot stand, it may be backed into a corner, forced to sit on its haunches, and have its front legs lifted while the corner prevents the dog from falling over. Alternatively, it may be fed on stairs so that it is at least at a 45-degree angle when eating. Feeding several small meals a day also helps prevent esophageal retention.

Some animals do better if fed dry or canned dog food free choice throughout the day from such a platform. It is impossible to predict whether a given dog will respond better to gruel or dry dog food. Therefore trial and error are necessary to determine the diet that works best for a particular animal. In some dogs the dilated esophagus may partially return to normal size and function. Even if the esophagus remains dilated, some dogs may be managed by dietary change and have a good quality of life.

Gastrostomy tubes bypass the csophagus and can provide some relief from regurgitation and/or aspiration. However, animals may still regurgitate saliva and, if there is gastroesophageal reflux, may also regurgitate food. Some animals



**FIG 31-1**Lateral contrast thoracic radiograph of a cat. Note large diverticulum suggestive of obstruction (arrows). This cat had generalized esophageal weakness without obstruction.

with gastrostomy tubes respond well for varying periods of time.

#### **Prognosis**

The prognosis is guarded to poor; some animals respond well, but most have severe regurgitation and/or aspiration symptoms despite all treatment efforts. Aspiration pneumonia is the major cause of death.

#### ACQUIRED ESOPHAGEAL WEAKNESS

# **Etiology**

Acquired esophageal weakness in dogs is usually caused by a neuropathy, myopathy, or junctionopathy (e.g., myasthenia gravis; see Box 28-5). German Shepherds, Golden Retrievers, and Irish Setters might have increased risk. In cats esophagitis may be a cause of acquired esophageal weakness.

#### **Clinical Features**

Acquired esophageal weakness primarily occurs in dogs. The patients usually are presented because of "vomiting" (actually regurgitation), but some present with a cough and little or no obvious regurgitation (e.g., regurgitated material is sometimes reswallowed or re-eaten by the animal). Weight loss may occur if the dog regurgitates most of its food.

#### Diagnosis

The initial diagnostic step is to document that regurgitation, rather than vomiting, is occurring (see p. 353). Acquired esophageal weakness is usually diagnosed by finding general-

ized esophageal dilation without evidence of obstruction on plain and contrast radiographs (see Fig. 29-3, *A*). The severity of clinical signs does not always correlate with the magnitude of radiographic changes. Some symptomatic animals have segmental weakness primarily affecting the cervical esophagus, just behind the cricopharyngeus muscle. However, normal dogs often have minimal amounts of barium retained in this location, so it is important to distinguish insignificant from clinically important retention. It is important to rule out lower esophageal spasm and stricture, which, though very rare, radiographically mimic esophageal weakness but require surgical treatment. Ideally, fluoroscopy should be used to look for evidence of gastroesophageal reflux, which may benefit from prokinetic therapy (e.g., cisapride).

It is important to search for underlying causes of acquired esophageal weakness (see Box 28-5). The titer of antibodies to acetylcholine receptors (indicative of myasthenia gravis) should be measured in dogs. "Localized" myasthenia may affect only the esophagus and/or oropharyngeal muscles. An adrenocorticotropic hormone (ACTH)-stimulation test is indicated to look for otherwise occult hypoadrenocorticism (even if serum electrolyte concentrations are normal). Serum thyroxine, free thyroxine, and thyroid-stimulating hormone (TSH) concentrations may reveal hypothyroidism, which can very rarely be associated with esophageal dysfunction. Tests of thyroid gland function must be interpreted carefully because of potential confusion regarding the euthyroid sick syndrome (see Chapter 51). Electromyography may reveal generalized neuropathies or myopathies. Dysautonomia occurs occasionally and is suspected on the basis of clinical signs (i.e., dilated colon, dry nose, dilated pupils, keratoconjunctivitis sicca, and/or bradycardia that responds poorly to atropine). Gastric outflow obstruction in cats can cause vomiting with secondary esophagitis. Other causes are rarely found (see Box 28-5). If an underlying cause cannot be found, the disease is termed *idiopathic acquired esophageal weakness* (i.e., idiopathic acquired megaesophagus).

#### Treatment

Dogs with acquired megaesophagus caused by localized myasthenia gravis or hypoadrenocorticism often respond to appropriate therapy (see Chapters 53 and 71). Localized myasthenia seems ultimately to respond best to immunosuppressive therapy (e.g., azathioprine), although pyridostigmine may help initially. Gastroesophageal reflux may respond to prokinetic and antacid therapy (cisapride at 0.25 mg/kg and omeprazole at 0.7 to 1.5 mg/kg are preferred). If the disease is idiopathic, conservative dietary therapy as described for congenital esophageal weakness is the only recourse. Although some dogs with congenital esophageal weakness regain variable degrees of esophageal function, this is rare in those with idiopathic acquired esophageal weakness. Severe esophagitis may cause secondary esophageal weakness, which resolves after appropriate therapy (discussed in more detail later in this chapter). Gastrostomy tubes diminish the potential for aspiration, ensure positive nitrogen balance, and help treat esophagitis if present. Some dogs benefit from the longterm use of a gastrostomy tube, but others continue to regurgitate and aspirate as a result of severe gastroesophageal reflux or simply the accumulation of large amounts of saliva in the esophagus.

#### **Prognosis**

All animals with acquired esophageal weakness are at risk for aspiration pneumonia and sudden death. If the underlying cause can be treated and the esophageal dilation and weakness can be resolved, the prognosis is good because the risk of aspiration is eliminated. The prognosis is guarded if the animal with idiopathic megaesophagus responds to dietary management (it is still at risk) and very poor if the animal does not respond to this protocol.

#### **ESOPHAGITIS**

#### Etiology

Esophagitis is principally caused by gastroesophageal reflux, persistent vomiting of gastric acid, esophageal foreign objects, and caustic agents. Pills (e.g., tetracycline) may be retained in the esophagus if they are not washed down with water or food and are thought to cause severe esophagitis in cats. An association between distal esophagitis (ostensibly caused by gastroesophageal reflux) and upper respiratory disease in brachycephalic dogs has been suggested.

#### **Clinical Features**

Regurgitation is expected, although anorexia and drooling may predominate if swallowing is painful. If a caustic agent (e.g., disinfectant) is ingested, the mouth and tongue are often hyperemic and/or ulcerated; anorexia is the primary sign.

# Diagnosis

A history of vomiting followed by both vomiting and regurgitation suggests esophagitis secondary to excessive exposure to gastric acid. This sign may occur in parvoviral enteritis and in various other disorders. Likewise, regurgitation or anorexia begining shortly after an anesthetic procedure may indicate esophagitis caused by reflux. Plain and contrast radiographs may reveal hiatal hernias, gastroesophageal reflux, or esophageal foreign bodies. Contrast esophagrams do not reliably detect esophagitis; esophagoscopy with or without biopsy is needed to establish a definitive diagnosis.

#### **Treatment**

Decreasing gastric acidity, preventing reflux of gastric contents into the esophagus, and protecting the denuded esophagus are the hallmarks of treatment. H2 receptor antagonists (see Table 30-4) may be used, but proton pump inhibitors (e.g., omeprazole) are superior for decreasing gastric acidity, a critical factor in these animals. However, because it may take 2 to 5 days for omeprazole to achieve maximum efficacy, famotidine may be used concurrently during initial therapy. Metoclopramide stimulates gastric emptying, resulting in less gastric volume to reflux into the esophagus, but cisapride (0.25 to 0.5 mg/kg) tends to be more effective. Sucralfate (particularly suspensions) might protect denuded esophageal mucosa (see Table 30-5), but its usefulness is unknown. Antibiotics effective against anaerobes (e.g., amoxicillin, clindamycin; see Drugs Used in Gastrointestinal Disorders, pp. 481-483) have been used but are of unknown value. A gastrostomy feeding tube helps to protect the esophagus while the mucosa is healing and ensures a positive nitrogen balance. Corticosteroids (e.g., prednisolone, 1.1 mg/kg/day) may be administered in an attempt to prevent cicatrix, but their efficacy is dubious. Hiatal hernias may need to be surgically repaired.

### Prognosis

The prognosis depends on the severity of the esophagitis and whether an underlying cause can be identified and controlled. Early, aggressive therapy helps to prevent cicatrix formation and allows a better prognosis.

## **HIATAL HERNIA**

# **Etiology**

Hiatal hernia is a diaphragmatic abnormality that allows part of the stomach (usually the cardia) to prolapse into the thoracic cavity. In severe cases it allows gastroesophageal reflux. The condition seems to be primarily congenital.

#### **Clinical Features**

Sharpei dogs seem to be predisposed to this disorder. Regurgitation is the primary sign in symptomatic individuals, but some animals are asymptomatic.

## **Diagnosis**

Plain radiographs or positive-contrast esophagrams may reveal gastric herniation into the thorax (Fig. 31-2); however, herniation may be intermittent and difficult to detect. It is sometimes necessary to put pressure on the abdomen during the radiographic procedure to cause displacement of the stomach during the study. Hiatal hernias are occasionally found endoscopically.

#### **Treatment**

If the hiatal hernia is symptomatic at an early age, surgery is more likely to be required to correct it. If signs of hiatal hernia first appear later in life, aggressive medical management of gastroesophageal reflux (e.g., cisapride, omeprazole) is often sufficient. If medical management is not successful, surgery can be considered.

## **Prognosis**

The prognosis is often good after surgical repair (congenital cases) or aggressive medical management (acquired cases).

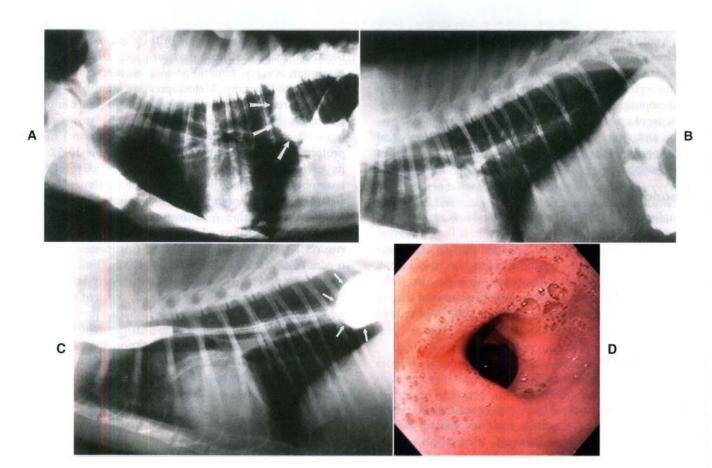
#### **DYSAUTONOMIA**

# **Etiology**

Dysautonomia in dogs and cats is an idiopathic condition that causes loss of autonomic nervous system function. In at least some circumstances, it may be due to a clostridial toxin.

#### **Clinical Features**

Clinical signs vary substantially. Megaesophagus and subsequent regurgitation are common (not invariable); however, dysuria and a distended urinary bladder, mydriasis and lack



#### FIG 31-2

**A,** Lateral radiograph of a dog with a hiatal hernia showing the gastric shadow extending cranial to the diaphragm (arrows). **B,** Lateral view of contrast esophagram of a cat with hiatal hernia. There is no evidence of hernia on this radiograph because it has apparently slid back into the abdomen. **C,** Lateral view of contrast esophagram of the cat in **B.** The body of the stomach has now slid into the thoracic cavity (arrows), confirming that a hiatal hernia is present. **D,** An endoscopic image of the lower esophageal sphincter (LES) area of a dog with a hiatal hernia. Gastric rugal folds can be seen. (**A,** Courtesy Dr. Russ Stickle, Michigan State University, East Lansing, Mich. **B** and **C,** Courtesy Dr. Royce Roberts, University of Georgia, Athens, Ga.)

of pupillary light response, dry mucous membranes, weight loss, constipation, vomiting, poor anal tone, and/or anorexia have all been reported. There appear to be geographic areas (e.g., Missouri and surrounding states) that currently have an increased incidence of the disease.

# **Diagnosis**

Dysautonomia is usually first suspected clinically by finding dysuria, dry mucous membranes, and abnormal pupillary light responses. Radiographs revealing distention of multiple areas of the alimentary tract (e.g., esophagus, stomach, small intestine) also are suggestive. A presumptive, antemortem diagnosis is usually made by observing the effects of pilocarpine on pupil size after 1 to 2 drops of 0.05% pilocarpine are placed in one eye only. Finding that the treated eye rapidly constricts whereas the untreated eye does not is consistent with dysautonomia. Similarly, finding that a dysuric dog with a large urinary bladder can urinate after subcutaneous administration of 0.04 mg bethanechol/kg is also suggestive (although not all affected animals respond). Definitive diagnosis requires histopathology of autonomic ganglia, which can be obtained only at necropsy.

#### **Treatment**

Treatment is palliative. Bethanechol can be given (1.25 to 5 mg once daily) to aid in urinary evacuation. The urinary bladder should be expressed as needed. Gastric prokinetics (e.g., cisapride) may help lessen vomiting. Antibiotics may be administered for aspiration pneumonia secondary to megaesophagus.

### **Prognosis**

The prognosis is usually grim.

#### **ESOPHAGEAL OBSTRUCTION**

## **VASCULAR RING ANOMALIES**

## **Etiology**

Vascular ring anomalies are congenital defects. An embryonic aortic arch persists, trapping the esophagus in a ring of tissue. Persistent right fourth aortic arch (PRAA) is the most commonly recognized vascular anomaly (see Chapter 5).

# **Clinical Features**

Vascular ring anomalies occur in both dogs and cats. Regurgitation is the most common presenting complaint, although signs of aspiration may occur. Clinical features often begin shortly after the animal eats solid food for the first time. Some animals have relatively minor clinical signs and are not diagnosed until they are several years old.

### **Diagnosis**

Definitive diagnosis is usually made by contrast esophagram (see Fig. 29-3, *B*). Typically, the esophagus cranial to the heart is dilated, whereas the esophagus caudal to the heart is

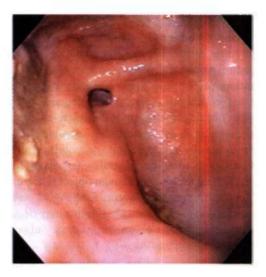


FIG 31-3
Endoscopic view of an esophageal lumen constricted by an extramural vascular ring anomaly.

normal. In rare cases the entire esophagus is dilated (the result of concurrent megaesophagus) except for a narrowing at the base of the heart. It has been suggested that if focal leftward deviation of the trachea is seen at the cranial border of the heart in the ventrodorsal or dorsoventral projections, this is sufficient to diagnose PRAA in young dogs that are regurgitating food. Endoscopically, the esophagus has an extramural narrowing (Fig. 31-3; i.e., not a mucosal proliferation or scar) near the base of the heart.

#### **Treatment**

Surgical resection of the anomalous vessel is necessary. Conservative dietary management (i.e., gruel diet) by itself is inappropriate because the dilation will persist and probably progress. In particular, the animal will be at risk for foreign body occlusion at the site of the PRAA. Dietary therapy may benefit some animals postoperatively.

#### **Prognosis**

Most patients improve dramatically after surgery. However, there are exceptions, and the more severe the preoperative dilation, the more likely regurgitation will continue postoperatively. Some dogs have concomitant esophageal weakness. A guarded prognosis is appropriate. If a postsurgical stricture occurs, esophageal ballooning or a second surgical procedure may be considered.

#### **ESOPHAGEAL FOREIGN OBJECTS**

#### Etiology

Almost anything may lodge in the esophagus, but objects with sharp points (e.g., bones, fishhooks) are probably most common. Most obstructions occur at the thoracic inlet, the base of the heart, or immediately in front of the diaphragm.

#### **Clinical Features**

Dogs are more commonly affected because of their less discriminating eating habits. Regurgitation or anorexia secondary to esophageal pain is common. Acute onset of regurgitation (as opposed to vomiting) is suggestive of esophageal foreign body. Clinical signs depend on where the obstruction occurs, whether it is complete or partial, and whether esophageal perforation has occurred. Complete obstructions cause regurgitation of solids and liquids, whereas partial obstructions may allow passage of liquids to the stomach. If an esophageal foreign object is impinging on airways, acute dyspnea may occur. Esophageal perforation usually causes fever and anorexia; dyspnea may occur as the result of pleural effusion or pneumothorax. Subcutaneous emphysema rarely occurs.

## **Diagnosis**

Plain thoracic radiographs reveal most esophageal foreign bodies (see Fig. 29-2), although the clinician may have to search carefully to find poultry bones or other food items that are even less radiodense. It is also important to look for evidence of esophageal perforation (i.e., pneumothorax, pleural effusion, fluid in the mediastinum). Esophagrams are rarely necessary; esophagoscopy is diagnostic and typically therapeutic.

#### **Treatment**

Foreign objects are best removed endoscopically unless (1) they are too firmly lodged to pull free or (2) radiographs suggest perforation. Thoracotomy is indicated in these two situations, although in rare cases perforations may be treated medically. Objects that cannot be moved should not be pulled on vigorously because of the risk of creating or enlarging a perforation. An object should be pushed into the stomach only when the clinician is confident that there are no sharp edges on the other side of the foreign object. During the procedure the esophagus should be insufflated carefully to avoid rupturing weakened areas or causing tension pneumothorax. After an object has been removed, the esophageal mucosa should be reexamined endoscopically to evaluate the damage caused by the object. Thoracic radiographs should be repeated to look for pneumothorax, an indication of perforation. Treatment after foreign body removal may include antibiotics, H<sub>2</sub> receptor antagonists or proton pump inhibitors, prokinetic agents, gastrostomy feeding tube, and/or corticosteroids (prednisolone, 1.1 mg/kg/day), depending on residual damage. Perforation usually requires thoracotomy to clean out septic debris and close the esophageal defect.

#### **Prognosis**

The prognosis for animals with esophageal foreign bodies without perforation is usually good, but the presence of perforation warrants a guarded prognosis depending on the severity of thoracic contamination. Cicatrix formation with obstruction is possible if substantial mucosal damage occurs.

## **ESOPHAGEAL CICATRIX**

## **Etiology**

Prior esophagitis from any cause may produce a stricture. Severe, deep inflammation of the esophagus (e.g., subsequent to foreign bodies or severe gastroesophageal reflux) is usually required for cicatrix to occur.

#### **Clinical Features**

Esophageal cicatrix occurs in both dogs and cats. The main sign is regurgitation (especially of solids). Some animals are clinically anorexic as a result of pain experienced when food becomes lodged at the stricture by forceful esophageal peristalsis.

# Diagnosis

Partial obstructions may be difficult to diagnose. Positive-contrast esophagrams (often using barium mixed with food) are necessary (Fig. 31-4). Esophagoscopy is definitive, but a partial stricture may not be obvious in large dogs unless the endoscopist is experienced and the esophagus is carefully inspected.

#### **Treatment**

Treatment consists of correcting the suspected cause (e.g., esophagitis) and/or widening the stricture by ballooning or bougienage. Surgical resection is not recommended because iatrogenic strictures at the anastomotic site are common. Ballooning is less traumatic, has less chance of perforation,

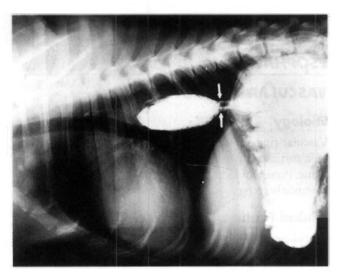


FIG 31-4

Lateral contrast esophagram using liquid barium mixed with moist food. Partial stricture (arrows) is preventing the bolus from readily entering the stomach. This stricture was not detected with barium paste, even when viewed fluoroscopically. However, when the barium-food mixture was used, the stricture was obvious and material was retained for minutes before passing. Endoscopically, there was a band of fibrous connective tissue at this spot.

and may be accomplished during esophagoscopy. Angioplasty catheters or esophageal dilation balloons are more useful than Foley catheters because the former are less likely to slide to one side of the obstruction during inflation. Bougienage can more easily cause a rupture, but it is relatively safe and equally effective if done by a trained individual. After the stricture has been dilated, antibiotics and/or corticosteroids (prednisolone, 1.1 mg/kg/day) are often administered to help prevent infection and stricture reformation; however, their efficacy is unknown. Intralesional steroid injections performed endoscopically have been tried in severe cases, but their value is uncertain at this time. If esophagitis is present, it should be treated aggressively. Some animals are cured after one ballooning, whereas others require multiple procedures.

Early identification and appropriate treatment of highrisk animals (i.e., those with severe esophagitis or after foreign object removal) help decrease the likelihood of stricture formation. Resolving esophagitis decreases inflammation and lessens fibrous connective tissue formation. The efficacy of corticosteroids is uncertain, but they are worth trying in selected cases.

#### **Prognosis**

The shorter the length of esophagus involved and the sooner the corrective procedure is performed, hopefully the better the prognosis. Animals with extensive, mature strictures and/or continuing esophagitis often need repeated dilatory procedures and have a more guarded prognosis. Most animals with benign esophageal strictures can be helped. Long-term gastrostomy tubes may be necessary in some animals.

#### **ESOPHAGEAL NEOPLASMS**

## Etiology

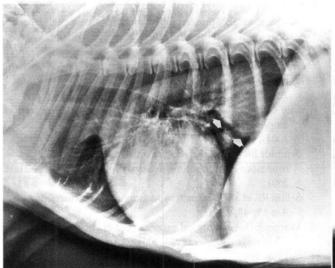
Primary esophageal sarcomas in dogs are often due to *Spirocerca lupi*. Primary esophageal carcinomas are of unknown etiology. Leiomyomas and leiomyosarcomas are found at the lower esophageal sphincter in older dogs. Thyroid carcinomas and pulmonary alveolar carcinomas may invade the esophagus in dogs. Squamous cell carcinomas are the most common esophageal neoplasm in cats.

#### **Clinical Features**

Dogs and cats with primary esophageal tumors may be asymptomatic until the tumor is far advanced, and these animals are diagnosed fortuitously when thoracic radiographs are obtained for other reasons. Regurgitation, anorexia, and/or fetid breath may occur if the tumor is large or causes esophageal dysfunction. If the esophagus is involved secondarily, clinical signs may result from esophageal dysfunction or tumor effects on other tissues.

# **Diagnosis**

Plain thoracic radiographs may reveal a soft tissue density in the caudal lung fields. These tumors may be difficult to discern radiographically from pulmonary lesions and usually require contrast esophagrams to make this distinction (Fig. 31-5). Esophagoscopy easily locates intraluminal and intramural masses (Fig. 31-6) or strictures and is sensitive in finding extraluminal masses causing esophageal stricture (i.e., the endoscopist will not be able to normally distend the esophageal lumen). Retroflexing the tip of an endoscope



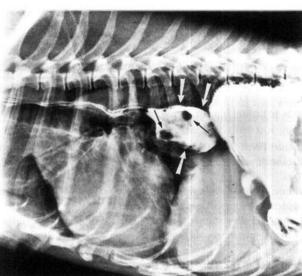


FIG 31-5

A, Lateral thoracic radiograph of a dog with a previously unsuspected mass (arrows) not obviously associated with the esophagus. B, Contrast esophagram in the same dog demonstrates that the esophagus is dilated (large arrows) and that there are intraesophageal filling defects (small arrows) in this dilated area. This dog had a primary esophageal carcinoma. (A from Allen D, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)

В



FIG 31-6

Endoscopic view of the lower esophageal sphincter of a dog. There is an intramural mass protruding into the lumen at 3 o'clock to the sphincter.

while it is within the stomach is the best method of identifying lower esophageal sphincter leiomyomas and leiomyosarcomas.

#### **Treatment**

Surgical resection is rarely curative (except for leiomyomas at the lower esophageal sphincter) because of the advanced nature of most esophageal neoplasms when they are diagnosed. Resection may be palliative. Photodynamic therapy may be beneficial in dogs and cats with small superficial esophageal neoplasms.

#### **Prognosis**

The prognosis is usually poor.

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\*Saunders\*\*

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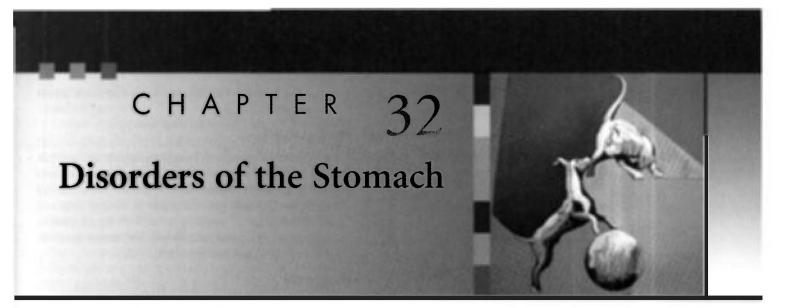
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# CHAPTER OUTLINE

#### **GASTRITIS**

Acute Gastritis
Hemorrhagic Gastroenteritis
Chronic Gastritis
Helicobacter-Associated Disease
Physaloptera rara
Ollulanus tricuspis

GASTRIC OUTFLOW OBSTRUCTION/ GASTRIC STASIS

Benign Muscular Pyloric Hypertrophy (Pyloric Stenosis) Gastric Antral Mucosal Hypertrophy Gastric Foreign Objects

Gastric Foreign Objects
Gastric Dilation/Volvulus

Partial or Intermittent Gastric Volvulus

Idiopathic Gastric Hypomotility Bilious Vomiting Syndrome

GASTROINTESTINAL ULCERATION/EROSION INFILTRATIVE GASTRIC DISEASES

Neoplasms Pythiosis

# **GASTRITIS**

# **ACUTE GASTRITIS**

## Etiology

Ingestion of spoiled or contaminated foods, foreign objects, toxic plants, chemicals, and/or irritating drugs (e.g., nonsteroidal antiinflammatory drugs [NSAIDs]) are common causes of acute gastritis. Infectious, viral, and bacterial causes occur but are not well defined in dogs and cats.

#### **Clinical Features**

Dogs are more commonly affected than cats by acute gastritis, probably because of their less discriminating eating

habits. Signs usually consist of acute onset of vomiting; food and bile are typically vomited, although small amounts of blood may be present. Affected animals are typically uninterested in food and may or may not feel sick. Fever and abdominal pain are uncommon.

# Diagnosis

Unless the animal was seen eating some irritative substance, acute gastritis is usually a presumptive diagnosis of exclusion based on history and physical examination findings. Abdominal imaging and/or clinical pathologic data are indicated if the animal is severely ill or if other disease is suspected. After alimentary foreign body, obstruction, parvoviral enteritis, uremia, diabetic ketoacidosis, hypoadrenocorticism, hepatic disease, hypercalcemia, and pancreatitis are ruled out, acute gastritis is a reasonable tentative diagnosis. If the anorexia/vomiting resolves after 1 to 2 days of symptomatic and supportive therapy, the tentative diagnosis is generally assumed to be correct (pancreatitis is still possible; see Chapter 40). Gastroscopy in such animals might reveal bile or gastric erosions/hyperemia.

Because acute gastritis is a diagnosis of exclusion and its signs are suggestive of various other disorders (e.g., foreign bodies, intoxication), good history taking and physical examination are mandatory. The owner should monitor the pet, and if the animal's condition worsens or does not improve within 1 to 3 days, imaging, a complete blood count (CBC), a serum biochemistry profile, and urinalysis are indicated.

#### **Treatment**

Parenteral fluid therapy and the withholding of food and water for 24 hours often suffice to control vomiting. If the vomiting persists or is excessive, or if the animal becomes depressed because of the vomiting, central-acting antiemetics (e.g., prochlorperazine, ondansetron, maropitant) may be administered parenterally (see p. 404). When feeding begins, small amounts of cool water are offered frequently. If the animal drinks without vomiting, small amounts of a bland diet (e.g., one part cottage cheese and two parts potato; one part boiled chicken and two parts potato) are offered. Antibiotics and corticosteroids are rarely indicated.

# **Prognosis**

The prognosis is excellent as long as the fluid and electrolyte balance is maintained.

#### **HEMORRHAGIC GASTROENTERITIS**

# Etiology

The cause of hemorrhagic gastroenteritis is unknown.

## **Clinical Features**

Hemorrhagic gastroenteritis occurs in dogs and is more severe than acute gastritis, typically causing profuse hematemesis and/or hematochezia. Classically occurring in smaller breeds that have not had access to garbage, this disorder has an acute course that can rapidly produce a critically ill animal. In severe cases the animal may be moribund by the time of presentation.

## Diagnosis

These animals are typically hemoconcentrated (i.e., packed cell volume  $[PCV] \ge 55\%$ ) with normal plasma total protein concentrations. The acute onset of typical clinical signs plus marked hemoconcentration allows a presumptive diagnosis. Thrombocytopenia and renal or prerenal azotemia may be seen in severely affected animals.

#### Treatment

Aggressive fluid therapy is initiated to treat or prevent shock, disseminated intravascular coagulation (DIC) secondary to hypoperfusion, and renal failure secondary to hypovolemia. Parenteral antibiotics (e.g., ampicillin, chloramphenicol; see pp. 481–483) are often used because of the fear that intestinal bacteria are proliferating, but their value has not been definitively established. If the patient becomes severely hypoalbuminemic during fluid therapy, synthetic colloids or plasma may be required.

### **Prognosis**

The prognosis is good for most animals that are presented in a timely fashion. Inadequately treated animals may die as a result of circulatory collapse, DIC, and/or renal failure.

### **CHRONIC GASTRITIS**

# Etiology

There are several types of chronic gastritis (e.g., lymphocytic/plasmacytic, eosinophilic, granulomatous, atrophic). Lymphocytic-plasmacytic gastritis might be an immune and/or inflammatory reaction to a variety of antigens. Helicobacter organisms might be responsible for such a reaction in some animals (especially cats). Physaloptera rara has seemingly been associated with a similar reaction in some dogs. Eosinophilic gastritis may represent an allergic reaction, probably to food antigens. Atrophic gastritis may be the result of chronic gastric inflammatory disease and/or

immune mechanisms. Ollulanus tricuspis may cause granulomatous gastritis in cats.

#### **Clinical Features**

Chronic gastritis appears to be more common in cats than in dogs and may or may not be associated with chronic enteritis (e.g., inflammatory bowel disease). Anorexia and vomiting are the most common signs in affected dogs and cats. The frequency of vomiting varies from once weekly to many times per day. Some animals have only anorexia, ostensibly as a result of low-grade nausea.

# Diagnosis

Clinical pathologic findings are not diagnostic, although eosinophilic gastritis inconsistently causes peripheral eosinophilia. Imaging sometimes documents mucosal thickening. Diagnosis requires gastric mucosal biopsy, and endoscopy is the most cost-effective method of obtaining these samples. Gastritis may be very localized, and endoscopy allows multiple biopsies over the entire mucosal surface, whereas surgical biopsy typically results in one sample that is taken blindly. Gastric biopsy should always be performed, regardless of the visual mucosal appearance. It must be remembered that enteritis is far more common than gastritis (which is why duodenal biopsies are usually more important than gastric biopsies). Gastric lymphoma can be surrounded by lymphocytic inflammation, and obtaining inappropriately superficial biopsy specimens may result in an incorrect diagnosis of inflammatory disease. Appropriate use of a scope with a 2.8-mm biopsy channel will usually prevent this misdiagnosis (unless the tumor is in the muscular layers of the stomach). Meaningful histopathologic interpretation of alimentary tissue can be difficult; the clinician should not hesitate to request a second histologic opinion if the diagnosis does not fit the patient or the response (or lack thereof) to therapy. If Ollulanus tricuspis is suspected, vomitus or gastric washings should be examined for the parasites, but they might also be found in gastric biopsy specimens. Physaloptera organisms are visible endoscopically.

#### Treatment

Lymphocytic-plasmacytic gastritis sometimes responds to dietary therapy (e.g., low-fat, low-fiber, elimination diets) alone (see p. 397). If such therapy is inadequate, corticosteroids (e.g., prednisolone, 2.2 mg/kg/day) can be used concurrently. Even if corticosteroids are required, dietary therapy may ultimately allow one to administer a substantially decreased dose, thus avoiding glucocorticoid adverse effects. If corticosteroid therapy is necessary, the dose should be gradually decreased to find the lowest effective dose. However, the dose should not be tapered too quickly after obtaining a clinical response or the clinical signs may return and be more difficult to control than they were initially. In rare cases, azathioprine or similar drugs will be necessary (see Chapter 30). Concurrent use of H<sub>2</sub> receptor antagonists is

sometimes beneficial. Ulceration should be treated as discussed on page 436.

Canine eosinophilic gastritis usually responds well to a *strict* elimination diet.If dietary therapy alone fails, corticosteroid therapy (e.g., prednisolone, 1.1 to 2.2 mg/kg/day) in conjunction with diet is usually effective. Feline hypereosinophilic syndrome responds poorly to most treatments.

Atrophic gastritis and granulomatous gastritis are more difficult to treat than lymphocytic-plasmacytic or canine eosinophilic gastritis. Diets low in fat and fiber (e.g., one part cottage cheese and two parts potato) may help control signs. Atrophic gastritis may respond to antiinflammatory, antacid, and/or prokinetic therapy; the latter is designed to keep the stomach empty, especially at night. Granulomatous gastritis is uncommon in dogs and cats and does not respond well to dietary or corticosteroid therapy.

# **Prognosis**

The prognosis for canine and feline lymphocytic-plasmacytic gastritis is often good with appropriate therapy. Some researchers have suggested that lymphoma has been known to develop in cats with lymphocytic gastritis; however, it is possible that the original diagnosis of lymphocytic gastritis was incorrect or that lymphoma developed independently of the gastritis.

The prognosis for canine eosinophilic gastritis is typically good. Feline eosinophilic gastritis can be a component of hypereosinophilic syndrome, which typically responds poorly to treatment. Hypereosinophilic syndrome has a guarded prognosis.

## HELICOBACTER-ASSOCIATED DISEASE

## **Etiology**

Helicobacter pylori is the principal spirochete found in human gastric mucosa, whereas Helicobacter felis, Helicobacter heilmannii, Helicobacter bizzozeronii, and Helicobacter salomonis may be the principal gastric spirochetes in dogs and cats. However, H. pylori has been found in cats.

## **Clinical Features**

People with symptomatic *H. pylori* infections usually develop ulceration and gastritis with neutrophilic infiltrates. They can also develop a lymphocytic lesion that is indistinguishable from lymphoma but that can be cured with antibiotic therapy. Dogs and cats with gastric *Helicobacter* infections may have nausea, anorexia, and/or vomiting associated with lymphocytic and occasionally neutrophilic infiltrates; however, most dogs and cats with gastric *Helicobacter* infections are asymptomatic. Because so many infected animals are asymptomatic, the cause and effect have not been clearly established between *Helicobacter* organisms and canine or feline gastric disease. Cats colonized with *H. pylori* seem to have more severe histologic lesions than those with *H. felis*, which in turn may be associated with more severe lesions than those with *H. heilmannii*. Reasonable anecdotal

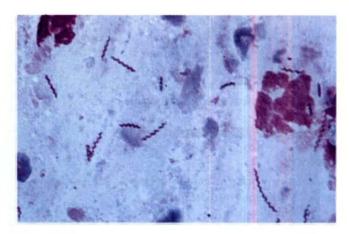


FIG 32-1
Air-dried smear of gastric mucosa obtained endoscopically and stained with Diff-Quik. Numerous spirochetes are seen. The affected dog was vomiting because of an ulcerated leiomyoma, and the spirochetes did not appear to be causing disease in this animal. (Magnification ×1000.)

evidence seems to suggest that some ill animals with gastric *Helicobacter* infections have their signs resolve when the organism is eliminated. Whether the "cure" is due to the elimination of *Helicobacter* organisms or something else remains in question, but it seems reasonable to assume that *Helicobacter* organisms cause disease in some animals.

# **Diagnosis**

Gastric biopsy is currently required for a diagnosis of *Helicobacter* infection. The organisms are easy to identify if the pathologist is looking for them and uses special stains (e.g., Giemsa, Warthin-Starry). The bacteria are not uniformly distributed throughout the stomach, and it is best to obtain biopsy specimens from the body, fundus, and antrum. The clinician may also diagnose this infection by cytologic evaluation of the gastric mucosa (Fig. 32-1) or by looking for gastric mucosal urease activity (see Chapter 29). Because of the uncertain pathogenicity of *Helicobacter* spp., the clinician is advised to look first for other, better explanations for the animal's clinical signs before deciding that a *Helicobacter* organism is causing disease.

#### **Treatment**

A combination of metronidazole, amoxicillin, and either famotidine or bismuth (either subsalicylate or subcitrate) seems to be effective in veterinary patients. Azithromycin and claritromycin have been substituted for bismuth in cats. Anecdotally, some animals seem to respond to just erythromycin or amoxicillin. Therapy should probably last for at least 10 days.

#### **Prognosis**

Animals with apparent *Helicobacter*-associated disease seem to respond well to treatment and have a good progno-

sis. However, because the cause and effect are uncertain, any animal that does not respond to therapy should be reexamined carefully to determine if other diseases are present. Recurrence of infection after treatment occurs, but it is not clear whether this represents a relapse of the original infection or reinfection from an outside sourse.

# PHYSALOPTERA RARA

## Etiology

Physaloptera rara is a nematode that has an indirect life cycle; beetles are the intermediate hosts.

#### **Clinical Features**

A single *Physaloptera rara* parasite can cause intractable vomiting. The parasite is primarily found in dogs. The vomiting usually does not resolve with antiemetics. Vomitus may or may not contain bile, and affected animals appear otherwise healthy.

# **Diagnosis**

Ova are seldom found in feces. Furthermore, sodium dichromate or magnesium sulfate solutions are usually necessary to identify the eggs in feces. Most diagnoses are made when the parasites are found during gastroduodenoscopy (see Fig. 29-25). There may be only one worm causing clinical signs, and it can be difficult to find, especially if it is attached within the pylorus. Alternatively, empirical treatment (as described here) is reasonable.

#### **Treatment**

Pyrantel pamoate or ivermectin is usually effective. If the parasite is found during endoscopy, it can be removed with forceps.

## **Prognosis**

The vomiting usually stops as soon as the worms are removed or eliminated.

## **OLLULANUS TRICUSPIS**

## Etiology

Ollulanus tricuspis is a nematode with a direct life cycle that is transmitted via vomited material.

#### **Clinical Features**

Cats are the most commonly affected species, although dogs and foxes are occasionally infected. Vomiting is the principal clinical sign, but clinically normal cats may harbor the parasite. Gross gastric mucosal lesions may or may not be seen in infested cats.

## Diagnosis

Cattery situations promote infection because the parasite is passed directly from one cat to another. However, occasionally cats with no known contact with other cats are infected. Looking for parasites in gastric washings or vomited material with a dissecting microscope is the best means of diagnosis. The parasite can be seen occasionally in gastric mucosal biopsy specimens.

# **Treatment/Prognosis**

Therapy is uncertain, but oxfendazole (10 mg/kg, orally administered q12h for 5 days) or fenbendazole might be effective. Occasionally, animals have severe gastritis and become debilitated.

# GASTRIC OUTFLOW OBSTRUCTION/ GASTRIC STASIS

# BENIGN MUSCULAR PYLORIC HYPERTROPHY (PYLORIC STENOSIS)

# Etiology

The cause of benign muscular pyloric hypertrophy has not been definitively established, although some experimental research suggests that gastrin promotes the development of pyloric stenosis.

# **Clinical Features**

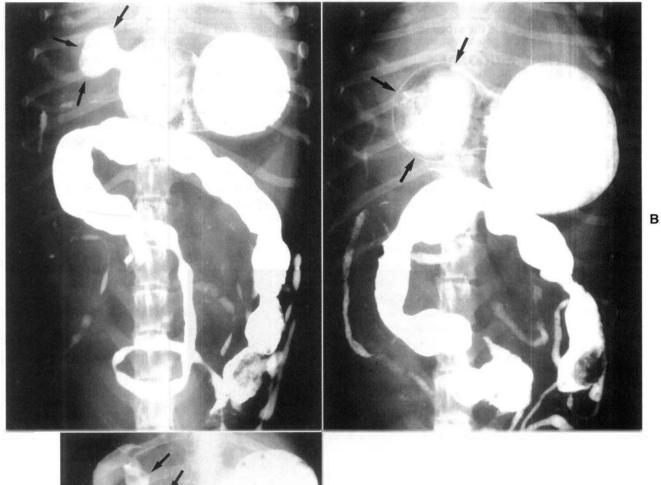
Benign muscular pyloric stenosis typically causes persistent vomiting in young animals (especially brachycephalic dogs and Siamese cats) but can be found in any animal. These animals usually vomit food shortly after eating. The vomiting is sometimes described as projectile. The animals are otherwise clinically normal, although some pets may lose weight. Some cats with pyloric stenosis vomit so much that secondary esophagitis, megaesophagus, and regurgitation occur, confusing the clinical picture. Hypochloremic, hypokalemic, metabolic alkalosis sometimes occurs, but it is inconsistent and nonspecific for gastric outflow obstruction.

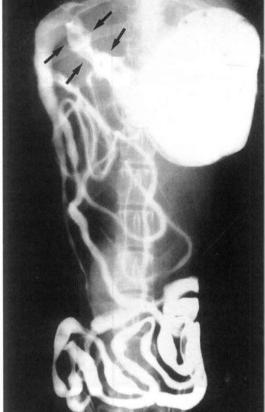
## Diagnosis

Diagnosing pyloric stenosis requires first finding gastric outflow obstruction during barium contrast-enhanced radiographs (Fig. 32-2), ultrasonography, gastroduodenoscopy, and/or exploratory surgery. Infiltrative disease of the pyloric mucosa then must be ruled out through biopsy. Endoscopically, the clinician may see prominent folds of normal-appearing mucosa at the pylorus. At surgery the serosa appears normal, but the pylorus is usually thickened when palpated. The surgeon can open the stomach and try to pass a finger through the pylorus to assess its patency. Extraalimentary tract diseases causing vomiting (see Box 28-6) should also be eliminated.

### **Treatment**

Surgical correction is indicated. Pyloroplasty (e.g., a Y-U-plasty) is more consistently effective than pyloromyotomy. However, improperly performed pyloroplasty or pyloromyotomy can cause perforation or obstruction. Furthermore, the clinician should not routinely do a pyloric outflow procedure whenever an exploratory procedure fails to reveal another cause of vomiting.





A

С

### FIG 32-2

A and B, Ventrodorsal contrast radiographs of a dog with a gastric outflow obstruction. These radiographs were obtained approximately 3 hours after barium administration. There is inadequate gastric emptying despite obvious peristalsis. Note the smooth contour of barium in the antrum (arrows), which is in contrast to C. This is a case of pyloric stenosis. C, Dorsoventral contrast radiographs of a dog with gastric adenocarcinoma. The antrum has an irregular outline but is not distended (arrows). This failure to distend persisted on multiple radiographs and indicates an infiltrative lesion.

## **Prognosis**

Surgery should be curative, and the prognosis is good.

# GASTRIC ANTRAL MUCOSAL HYPERTROPHY

# **Etiology**

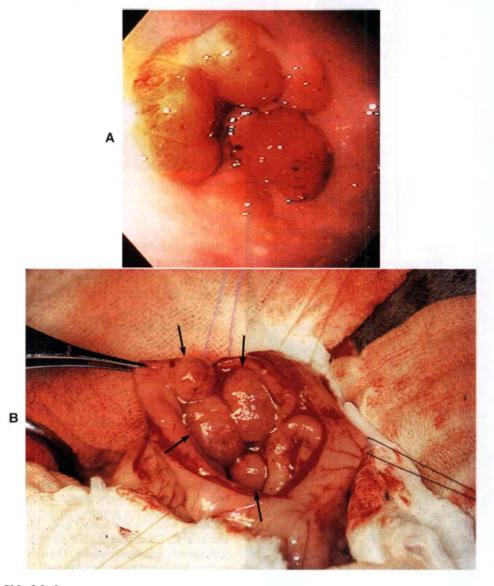
Antral mucosal hypertrophy is idiopathic. Gastric outflow obstruction is caused by excessive, nonneoplastic mucosa that occludes the distal gastric antrum (Fig. 32-3). This disorder is different from benign muscular pyloric stenosis, in which the mucosa is thrown up into folds secondary to the submucosal thickening.

#### **Clinical Features**

Principally found in older, small-breed dogs, antral hypertrophy clinically resembles pyloric stenosis (i.e., animals usually vomit food, especially after meals).

# **Diagnosis**

Gastric outlet obstruction is diagnosed radiographically, ultrasonographically, or endoscopically; however, definitive diagnosis of antral mucosal hypertrophy requires biopsy. Endoscopically, the antral mucosa is redundant and may resemble a submucosal neoplasm causing convoluted mucosal folds. In some cases the mucosa will be obviously reddened and inflamed. However, the mucosa in dogs with



**FIG 32-3 A,** Endoscopic view of the pyloric region of a dog that has gastric antral mucosal hypertrophy. If biopsy is not performed, these folds may easily be mistaken for neoplasia. **B,** Intraoperative photograph of a dog's opened pylorus. Note the numerous folds of mucosa that are protruding (arrows) as a result of gastric antral mucosal hypertrophy.

antral hypertrophy is usually not as firm or hard as expected in those with infiltrative carcinomas or leiomyomas. If antral mucosal hypertrophy is seen at surgery, there should be no evidence of submucosal infiltration or muscular thickening suggestive of neoplasia or benign pyloric stenosis, respectively. It is important to differentiate mucosal hypertrophy from these other diseases so that therapeutic recommendations are appropriate (e.g., gastric carcinomas typically have a worse prognosis, and surgery is not always indicated).

## **Treatment**

Antral mucosal hypertrophy is treated by mucosal resection, usually combined with pyloroplasty. Pyloromyotomy alone may be insufficient to resolve clinical signs from mucosal hypertrophy.

## **Prognosis**

The prognosis is excellent.

#### **GASTRIC FOREIGN OBJECTS**

## **Etiology**

Objects that can pass through the esophagus may become a gastric or intestinal foreign object. Subsequently, vomiting may result from gastric outlet obstruction, gastric distention, or irritation. Linear foreign objects whose orad end lodges at the pylorus may cause intestinal perforation with subsequent peritonitis and must be dealt with expeditiously (see the section on intestinal obstruction on p. 464).

# **Clinical Features**

Dogs are affected more commonly than cats because of their less discriminating eating habits. Vomiting (not regurgitation) is a common sign, but some animals demonstrate only anorexia, whereas others are asymptomatic.

# Diagnosis

Acute onset of vomiting in an otherwise normal animal, especially a puppy, suggests foreign body ingestion. The clinician might palpate an object during physical examination or see it during plain radiographic imaging. Imaging and endoscopy are the most reliable means of diagnosis. However, diagnosis can be difficult if the stomach is filled with food. Some diseases closely mimic obstruction caused by foreign objects; canine parvovirus may initially cause intense vomiting, during which time viral particles might not be detected in the feces. Hypokalemic, hypochloremic, metabolic alkalosis is consistent with gastric outflow obstruction; however, these changes may be absent in animals with gastric obstruction and present in animals without obstruction. Therefore these electrolyte changes are neither sensitive nor specific for gastric outflow obstruction.

## Treatment

Small foreign objects that are unlikely to cause trauma may pass through the gastrointestinal tract. If there is doubt, it is best to remove the object in question. Vomiting can be induced (e.g., apomorphine in the dog, 0.02 or 0.1 mg/kg administered intravenously or subcutaneously, respectively; hydrogen peroxide in the dog, 1 to 5 ml of 3% solution/kg administered orally; xylazine in the cat, 0.4 to 0.5 mg/kg administered intravenously) to eliminate gastric foreign objects if the clinician believes that the object will not cause problems during forcible ejection (i.e., it does not have sharp edges or points and is small enough to pass easily). If there is doubt as to the safety of this approach, the object should be removed endoscopically or surgically.

Before the animal is anesthetized for surgery or endoscopy, the electrolyte and acid-base status should be evaluated. Although electrolyte changes (e.g., hypokalemia) are common, they are impossible to predict with any accuracy. Hypokalemia predisposes to cardiac arrhythmias and should be corrected before anesthesia is induced.

Endoscopic removal of foreign objects requires a flexible endoscope and appropriate retrieval forceps. The animal should always be radiographed just before being anesthetized to ensure that the object is still in the stomach. Laceration of the esophagus and entrapment of the retrieval forceps in the object should be avoided. If endoscopic removal is unsuccessful, gastrostomy should be performed.

## **Prognosis**

The prognosis is usually good unless the animal is debilitated or there is septic peritonitis secondary to gastric perforation.

# **GASTRIC DILATION/VOLVULUS**

# **Etiology**

The cause of gastric dilation/volvulus (GDV) is unknown but may involve abnormal gastric motility. Thoracic confirmation seems correlated with risk; Irish Setters with a deeper thorax relative to width are more likely to experience GDV. Dogs with parents that had GDV may also be at increased risk. There are conflicting data regarding what predisposes dogs to GDV. Eating a large volume during a meal, eating once a day, eating rapidly, being underweight, eating from an elevated platform, being male, and advanced age seem to increase risk. Feeding dry food that is high in oil may also increase risk. GDV occurs when the stomach dilates excessively with gas (e.g., aerophagia, bacterial fermentation of carbohydrates, diffusion from the blood). The stomach may maintain its normal anatomic position (gastric dilation) or twist (GDV). In the latter situation the pylorus typically rotates ventrally from the right side of the abdomen below the body of the stomach to become positioned dorsal to the gastric cardia on the left side. If the stomach twists sufficiently, gastric outflow is obstructed and progressive distention with air results. Splenic torsion may occur concurrently with the spleen on the right side of the abdomen if the stomach twists sufficiently. Massive gastric distention obstructs the hepatic portal vein and posterior vena cava, causing mesenteric congestion, decreased cardiac output, severe shock, and DIC. The gastric blood supply may be impaired, causing gastric wall necrosis.

# **Clinical Features**

GDV principally occurs in large- and giant-breed dogs with deep chests; it rarely occurs in small dogs or cats. Affected dogs typically retch nonproductively and may demonstrate abdominal pain. Marked anterior abdominal distention may be seen later. However, abdominal distention is not always obvious in large, heavily muscled dogs. Eventually, depression and a moribund state occur.

## **Diagnosis**

Physical examination findings (i.e., a large dog with a large tympanic anterior abdomen that is retching unproductively) allow presumptive diagnosis of GDV but do not permit differentiation between dilation and GDV; plain abdominal radiographs, preferably with the animal in right lateral recumbency, are required. Volvulus is denoted by displacement of the pylorus and/or formation of a "shelf" of tissue in the gastric shadow (Fig. 32-4). It is impossible to distinguish between dilation and dilation/torsion on the basis of ability or inability to pass an orogastric tube.

#### **Treatment**

Treatment consists of initiating aggressive therapy for shock (hetastarch or hypertonic saline infusion [see p. 396] may make treatment for shock quicker and easier) and then decompressing the stomach unless the patient is asphyxiating, in which case the stomach is decompressed first. Gastric

decompression is usually performed with an orogastric tube, after which the stomach is lavaged with warm water to remove its contents. The stomach of dogs with dilation and many with GDV can be decompressed in this manner. Mesenteric congestion caused by the enlarged stomach predisposes to infection and endotoxemia, making systemic antibiotic administration reasonable (e.g., cefazolin, 20 mg/kg administered intravenously). Serum electrolyte concentrations and acid-base status should be evaluated.

The orogastric tube should not be forced into the stomach against undue resistance because it could rupture the lower esophagus. If the tube cannot be passed into the stomach, the clinician may insert a large needle (e.g., a 3-inch, 12- to 14-gauge needle) into the stomach just behind the rib cage in the left flank to decompress the stomach (which usually causes some abdominal contamination) or perform a temporary gastrostomy in the left paralumbar area (i.e., the stomach wall is sutured to the skin, and then the stomach wall is incised to allow evacuation of accumulated gas and other contents). After the animal is stabilized, a second procedure is performed to close the temporary gastrostomy (if present), reposition the stomach, remove the spleen (if grossly infarcted), remove or invaginate the devitalized gastric wall, and perform a gastropexy. Gastropexy (e.g., circumcostal, belt loop, tube gastrostomy) is recommended to help prevent recurrence of torsion and may be correlated with prolongation of survival. Another option consists of

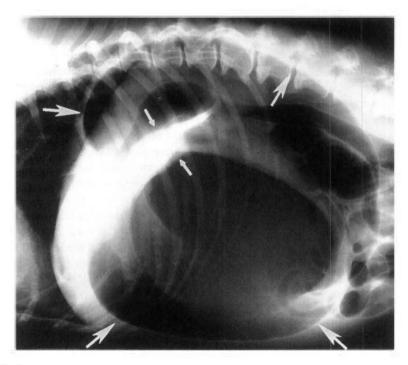


FIG 32-4

Lateral radiograph of a dog with gastric dilation/volvulus. The stomach is dilated (large arrows), and there is a "shelf" of tissue (small arrows), demonstrating that the stomach is malpositioned. Radiographs obtained from the right lateral position seem superior to those of other views in demonstrating this shelf. If the stomach were similarly distended but not malpositioned, the diagnosis would be gastric dilation.

immediately performing a laparotomy after decompressing the stomach but before stabilizing the animal. The decision as to whether to first stabilize the animal or immediately perform surgery is based on the condition of the dog at initial presentation and on whether the animal would be a considerably better anesthetic risk after stabilization.

If the dog has GDV (see Fig. 32-4), surgery is necessary to reposition the stomach; this is followed by gastropexy to prevent recurrence. This surgery should be performed as soon as the animal constitutes an acceptable anesthetic risk because torsion (even when the stomach is deflated) impairs gastric wall perfusion and may cause necrosis. Areas of gastric wall necrosis should be resected, or preferably invaginated, to prevent perforation and abdominal contamination. In dogs with gastric dilation without torsion, gastropexy is optional and may be performed after the dog is completely recovered from the current episode. Gastropexy almost always prevents torsions but does not prevent dilation.

Postoperatively, the animal should be monitored by electrocardiogram (ECG) for 48 to 72 hours. Lidocaine, procainamide, and/or soltolol therapy may be needed if cardiac arrhythmias diminish cardiac output (see Chapter 4). Hypokalemia is common and makes such arrhythmias refractory to medical control. Therefore hypokalemia should be resolved.

Prevention is difficult because the cause is unknown. Although preventing exercise after meals and feeding small meals of softened food would seem to be useful, there are no data to confirm this speculation.

# **Prognosis**

The prognosis depends on how quickly the condition is recognized and treated. Mortality rates ranging from 20% to 45% have been reported. Early therapy improves the prognosis, whereas a delay lasting more than 5 hours between onset of signs and presentation to the veterinarian's office, hypothermia at admission, preoperative cardiac arrhythmias, increased preoperative blood lactate concentrations, gastric wall necrosis, severe DIC, partial gastrectomy, splenectomy, and postoperative development of acute renal failure seem to worsen the prognosis. Although rare, gastric dilation may recur after gastropexy. Prophylactic gastropexy may be elected for animals believed to be at increased risk for GDV. Laparoscopy can be used to make prophylactic gastropexy a minimally invasive procedure.

# PARTIAL OR INTERMITTENT GASTRIC VOLVULUS

#### Etiology

The causes for partial and intermittent gastric volvulus might be the same as for classic GDV.

#### **Clinical Features**

Dogs with partial or intermittent volvulus do not have the life-threatening, progressive syndrome characterizing classic GDV. Although occurring in the same breeds as GDV, partial gastric volvulus usually produces a chronic, intermittent, potentially difficult-to-diagnose problem. It may occur repeatedly and spontaneously resolve; dogs may appear normal between bouts. Some dogs have persistent, nondistended volvulus and are asymptomatic.

## **Diagnosis**

Plain radiographs are usually diagnostic (Fig. 32-5). However, diagnosis may require repeated radiographs and/or contrast studies. Chronic volvulus will rarely be diagnosed endoscopically. It is possible, in rare cases, to cause a temporary gastric volvulus by manipulating the gastroscope in an air-distended stomach. Therefore the clinician must differentiate spontaneous from iatrogenic volvulus.

#### **Treatment**

If partial or intermittent gastric volvulus is diagnosed, surgical repositioning and gastropexy are usually curative.

# **Prognosis**

The prognosis is usually good once the problem is identified and surgically corrected.

# IDIOPATHIC GASTRIC HYPOMOTILITY

## Etiology

Idiopathic gastric hypomotility refers to an anecdotal syndrome characterized by poor gastric emptying and motility despite the lack of anatomic obstruction, inflammatory lesions, or other causes.

#### **Clinical Features**

Idiopathic gastric hypomotility has primarily been diagnosed in dogs. Affected dogs usually vomit food several hours after eating but otherwise feel well. Weight loss may or may not occur.

## Diagnosis

Fluoroscopic studies document decreased gastric motility, but diagnosis requires ruling out gastric outlet obstruction, infiltrative bowel disease, inflammatory abdominal disease, and extraalimentary tract diseases (e.g., renal, adrenal, or hepatic failure; severe hypokalemia or hypercalcemia).

#### **Treatment**

Metoclopramide (see Table 30-3) increases gastric peristalsis in some but not all affected dogs. Cisapride or erythromycin may be effective if metoclopramide fails. Diets low in fat and fiber promote gastric emptying and may be helpful.

## **Prognosis**

Dogs that respond to medical management have a good prognosis. Those that do not respond have a poor prognosis for cure, although they may still be acceptable pets.



FIG 32-5
Lateral abdominal radiograph of an Irish Setter with chronic vomiting caused by gastric volvulus that did not cause dilation. A "shelf" of tissue (arrows) demonstrates that the stomach has twisted.

# **BILIOUS VOMITING SYNDROME**

# **Etiology**

Bilious vomiting syndrome appears to be caused by gastroduodenal reflux that occurs when the dog's stomach is empty for long periods of time (e.g., during an overnight fast).

#### **Clinical Features**

Bilious vomiting syndrome usually affects otherwise normal dogs that are fed once daily in the morning. Classically, the pet vomits bile-stained fluid once a day, usually late at night or in the morning just before eating.

### **Diagnosis**

The clinician must rule out obstruction, gastrointestinal inflammation, and extraalimentary tract diseases. Elimination of these disorders, in addition to the history as described, strongly suggests bilious vomiting syndrome.

#### **Treatment**

Feeding the dog an extra meal late at night to prevent the stomach from being empty for long periods of time is often curative. If vomiting continues, a gastric prokinetic may be administered late at night to prevent reflux.

### **Prognosis**

The prognosis is excellent. Most animals respond to therapy, and those that do not remain otherwise healthy.

# GASTROINTESTINAL ULCERATION/ EROSION

#### Etiology

Gastrointestinal ulceration/erosion (GUE) is more common in dogs than in cats. There are several potential causes. Stress ulceration is associated with severe hypovolemic, septic, or neurogenic shock, such as occurs after trauma, surgery, and endotoxemia. These ulcers are typically in the gastric antrum, body, and/or duodenum. Extreme exertion (e.g., in sled dogs) causes gastric erosions/ulcers in the body and fundus, probably as a result of a combination of poor perfusion and high circulating levels of glucocorticoids.

NSAIDs (e.g., aspirin, ibuprofen, naproxen, piroxicam, flunixin) are a major cause of canine GUE because these drugs have longer half-lives in dogs than in people. Naproxen, ibuprofen, indomethacin, and flunixin are particularly dangerous to dogs. Concurrent use of more than one NSAID or use of an NSAID plus a corticosteroid (especially dexamethasone) increases the risk of GUE. The newer COX-2-selective NSAIDs (e.g., carprofen, dericoxib, meloxicam, etodolac) are less likely to cause GUE; however, GUE can still occur if these drugs are used inappropriately (e.g., excessive dose, failure to have an adequate washout period between use of different NSAIDs, concurrent use of corticosteroids). Use of NSAIDs in animals with poor visceral perfusion (e.g., those in cardiac failure, shock) may also increase the risk of GUE. Most steroids pose minimal risk unless the

animal is otherwise at increased risk for GUE (e.g., anoxic gastric mucosa due to shock or anemia). Dexamethasone, however, is clearly ulcerogenic when used at high doses.

Mast cell tumors may release histamine (especially if radiation or chemotherapy is being used), which induces gastric acid secretion. Gastrinomas are apudomas principally found in the pancreas. Usually occurring in older dogs and rarely in cats, these tumors secrete gastrin, which produces severe gastric hyperacidity, duodenal ulceration, esophagitis, and diarrhea.

Renal failure seldom causes GUE, but hepatic failure seems to be an important cause in dogs. Foreign objects rarely cause GUE, but they prevent healing and increase blood loss from ulcers. Inflammatory bowel disease may be associated with GUE in dogs, although most animals with this condition do not have these lesions. Gastric neoplasms and other infiltrative diseases (e.g., pythiosis) may also cause GUE (see p. 438) Tumors are especially important as a cause in cats and older dogs.

### **Clinical Features**

GUE is more common in dogs than in cats. Anorexia may be the principal sign. If vomiting occurs, blood (i.e., fresh or digested) may or may not be present. Anemia and/or hypoproteinemia occasionally occur and cause signs (i.e., edema, pale mucous membranes, weakness, dyspnea). Melena may occur if there is severe blood loss within a short period of time. Most affected dogs, even those with severe GUE, do not demonstrate pain during abdominal palpation. Perforation is associated with signs of septic peritonitis (see p. 476). Some ulcers perforate and seal over before generalized peritonitis occurs. In such cases a small abscess may develop at the site, causing abdominal pain, anorexia, and/or vomiting.

### **Diagnosis**

A presumptive diagnosis of GUE is usually based on finding evidence of gastrointestinal blood loss (e.g., hematemesis, melena, iron-deficiency anemia) in an animal without a coagulopathy. The history and physical examination may identify an obvious cause (e.g., stress, NSAID administration, mast cell tumor). Perforation may cause peritonitis and signs of an acute abdomen and sepsis. Because mast cell tumors may resemble almost any cutaneous lesion, all cutaneous masses or nodules should be evaluated cytologically. Hepatic failure is usually diagnosed on the basis of the serum biochemistry profile. Contrast radiographs are diagnostic for foreign objects and sometimes for GUE (Fig. 32-6). Ultrasonography sometimes detects gastric thickening (such as would be seen in infiltrated lesions) and/or mucosal defects. Endoscopy is the most sensitive and specific tool for diagnosing GUE (see Figs. 29-18 to 29-21) and, in conjunction with biopsy, can be used to diagnose tumors (see Fig. 29-20), foreign bodies (see Fig. 29-24), and inflammation that may cause ulcers. Endoscopic findings may also suggest a gastrinoma if duodenal erosions are found. Serum gastrin concentrations should be measured if a gastrinoma is suspected or if there are no other likely causes.



FIG 32-6

Contrast ventrodorsal radiograph of a dog with persistent vomiting. Note the small "sliver" representing retention of barium in the region of the pylorus (arrows). This area of contrast persisted on several radiographs. Endoscopy and surgery confirmed a large ulcer that had perforated and spontaneously sealed. This radiograph demonstrates how difficult radiographic diagnosis of gastrointestinal ulceration can be.

## **Treatment**

Therapy depends on the severity of GUE and whether an underlying cause is detected. Animals with suspected GUE that is not obviously life threatening (i.e., there is no evidence of severe anemia, shock, sepsis, severe abdominal pain, or severe depression) may first be treated symptomatically if the clinician believes that he or she knows the cause.

Symptomatic therapy (e.g., H<sub>2</sub> receptor antagonists, proton pump inhibitors, sucralfate, parenteral fluids, withholding food) is often successful. Eliminating the underlying etiology (e.g., NSAIDs, shock) is important, and any gastric foreign objects present should be removed. If appropriate medical therapy is unsuccessful after 5 or 6 days, or if the animal has life-threatening bleeding despite appropriate medical therapy, the ulcer(s) should usually be resected. The stomach should be examined endoscopically before surgery to determine the number and location of the ulcers; it is surprisingly easy to miss ulcers during laparotomy.

In animals with gastrinomas,  $H_2$ -receptor antagonist therapy is often palliative for months. Animals with high serum gastrin concentrations may require more potent and/or higher doses of  $H_2$  receptor antagonists (e.g., famotidine) or the more potent proton pump inhibitors (see Table 30-4).

Prevention of GUE is preferable to treatment, and rational NSAID and steroid therapy are especially important. Sucralfate (Carafate; see Table 30-5) and H<sub>2</sub> receptor antagonists (see Table 30-4) have been used in an attempt to prevent GUE in dogs receiving NSAIDs and steroids; however, there is no good evidence that these drugs are effective for this purpose in dogs and cats. Misoprostol (see Table 30-5) is designed to prevent NSAID-induced ulceration and is more effective than H<sub>2</sub> receptor antagonists or sucralfate. However, it is not uniformly successful.

# **Prognosis**

The prognosis is favorable if the underlying cause can be controlled and if therapy prevents perforation of the ulcer.

### INFILTRATIVE GASTRIC DISEASES

#### **NEOPLASMS**

## Etiology

Neoplastic infiltrations (e.g., adenocarcinoma, lymphoma, leiomyomas, and leiomyosarcomas in dogs; lymphoma in cats) may produce GUE through direct mucosal disruption. Gastric lymphoma is typically a diffuse lesion but can produce masses. The cause and significance of benign gastric polyps are unknown. They seem to occur more commonly in the antrum.

# **Clinical Features**

Dogs and cats with gastric tumors are usually asymptomatic until the disease is advanced. Anorexia (not vomiting) is the most common initial sign. Vomiting caused by gastric neoplasia usually signifies advanced disease or gastric outflow obstruction. Adenocarcinomas are typically infiltrative and decrease emptying by impairing motility and/or obstructing the outflow tract. Weight loss is commonly caused by nutrient loss or cancer cachexia syndrome. Hematemesis occasionally occurs, but leiomyomas seem to be the tumor most likely to cause severe acute upper gastrointestinal bleeding. Other bleeding gastric tumors are more likely to cause iron deficiency anemia even if gastrointestinal blood loss is not obvious. Polyps rarely cause signs unless they obstruct the pylorus.

## Diagnosis

Iron deficiency anemia in a dog or cat without obvious blood loss suggests gastrointestinal bleeding, often caused by a tumor. Plain and contrast imaging may reveal gastric wall thickening, decreased motility, and/or mucosal irregularities. The only sign of submucosal adenocarcinoma may be failure of one area to dilate (see Fig. 32-2, C). Ultrasound-guided aspiration of thickened areas in the gastric wall may produce cytologic preparations that are diagnostic for adenocarcinoma or lymphoma. Endoscopically, such areas may appear as multiple mucosal folds extending into the lumen without ulceration or erosion. Some tumors will be obvious endo-

scopically. When biopsy of such lesions is performed endoscopically, the sample must be deep enough to ensure that submucosal tissue is included. Furthermore, scirrhous adenocarcinomas may be so dense that the clinician cannot obtain diagnostic biopsy specimens with flexible endoscopic forceps. Mucosal lymphomas and nonscirrhous adenocarcinomas often produce GUE, and endoscopically obtained tissue samples are usually diagnostic. Polyps are usually obvious endoscopically, but a biopsy specimen should always be obtained and evaluated to ensure that adenocarcinoma is not present.

#### **Treatment**

Most adenocarcinomas are advanced before clinical signs are obvious, making complete surgical excision difficult or impossible. Leiomyomas and leiomyosarcomas are more likely to be resectable than adenocarcinomas. Gastroduodenostomy may palliate gastric outflow obstruction caused by an unresectable tumor. Chemotherapy is rarely helpful except for dogs and cats with lymphoma.

## **Prognosis**

The prognosis for adenocarcinomas and lymphomas is poor unless they are detected very early. Leiomyomas and leiomyosarcomas, if diagnosed relatively early, are often cured surgically. It does not appear to be necessary to resect gastric polyps unless they are causing outflow obstruction.

### **PYTHIOSIS**

## Etiology

Pythiosis is a fungal infection caused by *Pythium insidiosum*. This species is principally found in the Gulf coast area of the southeastern United States. Any area of the alimentary tract or skin may be affected. The fungus typically causes intense submucosal infiltration of fibrous connective tissue and a purulent, cosinophilic, granulomatous inflammation causing GUE. Such infiltration prevents peristalsis, causing stasis.

## **Clinical Features**

Pythiosis principally affects dogs, typically causing vomiting, anorexia, diarrhea, and/or weight loss. Because gastric outflow obstruction occurs frequently, vomiting is common. Colonic involvement may cause tenesmus and hematochezia.

## Diagnosis

Diagnosis requires serology or seeing the organism cytologically or histologically. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) tests are available to look for antibodies or antigen, respectively. Biopsy samples should include the submucosa because the organism is more likely to be there than in the mucosa. Such diagnostic biopsy specimens can be procured by way of rigid endoscopy; however, because of the dense nature of the infiltrate, a sufficiently deep sample can rarely be obtained by flexible endoscopy. Cytologic analysis of a tissue sample obtained by scraping an excised piece of submucosa with a

scalpel blade may be diagnostic; fungal hyphae that do not stain and appear as "ghosts" with typical Romanowsky-type stains are strongly supportive of a diagnosis. The organisms may be sparse and difficult to find histologically, even in large tissue samples.

#### **Treatment**

Complete surgical excision provides the best chance for cure. Itraconazole (5 mg/kg administered orally q12h) or liposomal amphotericin B (2.2 mg/kg/treatment) with or without terebinifin may benefit some animals for varying periods of time. Immunotherapy has recently become available, but critical evaluation of the efficacy of this therapy is not currently available

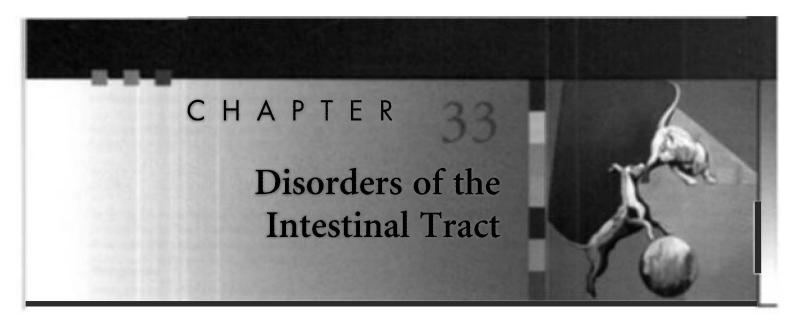
## **Prognosis**

Pythiosis often spreads to or involves structures that cannot be surgically removed (e.g., root of the mesentery, pancreas surrounding the bile duct), resulting in a grim prognosis.

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# **CHAPTER OUTLINE**

# **ACUTE DIARRHEA**

**Acute Enteritis** 

Enterotoxemia

Dietary-Induced Diarrhea

#### INFECTIOUS DIARRHEA

Canine Parvoviral Enteritis

Feline Parvoviral Enteritis

Canine Coronaviral Enteritis

Feline Coronaviral Enteritis

Feline Leukemia Virus-Associated Panleukopenia

(Myeloblastopenia)

Feline Immunodeficiency Virus-Associated

Diarrhea

Salmon Poisoning/Elokomin Fluke Fever

# BACTERIAL DISEASES: COMMON THEMES

Campylobacteriosis

Salmonellosis

Clostridial Diseases

Miscellaneous Bacteria

Histoplasmosis

Protothecosis

# ALIMENTARY TRACT PARASITES

Whipworms

Roundworms

Hookworms

Tapeworms

Strongyloidiasis

Coccidiosis

Cryptosporidia

Giardiasis

Trichomoniasis

Heterobilharzia

## MALDIGESTIVE DISEASE

**Exocrine Pancreatic Insufficiency** 

### MALABSORPTIVE DISEASES

Antibiotic-Responsive Enteropathy

Dietary-Responsive Disease

Small Intestinal Inflammatory Bowel Disease

Large Intestinal Inflammatory Bowel Disease

Granulomatous Enteritis/Gastritis

Immunoproliferative Enteropathy in Basenjis

Enteropathy in Chinese Shar-Peis

## PROTEIN-LOSING ENTEROPATHY

Causes of Protein-Losing Enteropathy

Intestinal Lymphangiectasia

Protein-Losing Enteropathy in Soft-Coated Wheaten

Terriers

## **FUNCTIONAL INTESTINAL DISEASE**

Irritable Bowel Syndrome

## INTESTINAL OBSTRUCTION

Simple Intestinal Obstruction

Incarcerated Intestinal Obstruction

Mesenteric Torsion/Volvulus

Linear Foreign Objects

Intussusception

#### MISCELLANEOUS INTESTINAL DISEASES

Short Bowel Syndrome

# NEOPLASMS OF THE SMALL INTESTINE

Alimentary Lymphoma

Intestinal Adenocarcinoma

Intestinal Leiomyoma/Leiomyosarcoma

# INFLAMMATION OF THE LARGE INTESTINE

Acute Colitis/Proctitis

Chronic Colitis

# INTUSSUSCEPTION/PROLAPSE OF THE LARGE INTESTINE

INITALINE

Cecocolic Intussusception

Rectal Prolapse

# NEOPLASMS OF THE LARGE INTESTINE

Adenocarcinoma

Rectal Polyps

### MISCELLANEOUS LARGE INTESTINAL DISEASES

**Pythiosis** 

# PERINEAL/PERIANAL DISEASES

Perineal Hernia

Perianal Fistulae

**Anal Sacculitis** 

#### PERIANAL NEOPLASMS

Anal Sac (Apocrine Gland) Adenocarcinoma Perianal Gland Tumors

#### CONSTIPATION

Pelvic Canal Obstruction Caused by Malaligned Healing of Old Pelvic Fractures Benign Rectal Stricture Dietary Indiscretion Leading to Constipation Idiopathic Megacolon

# ABBREVIATIONS USED IN THE CHAPTER

**ARE:** Antibiotic-responsive enteropathy (previously known as *small intestinal bacterial overgrowth—IBO*)

CPV: Canine parvovirus

EGE: Eosinophilic gastroenteritis

**EHEC:** Enterohemorrhagic *Escherichia coli* E**PI:** Exocrine pancreatic insufficiency

FeLV: Feline leukemia virus

FIV: Feline immunodeficiency virus GDV: Gastric dilation and volvulus GUE: Gastric ulceration/erosion HES: Hypereosinophilic syndrome IBD: Inflammatory bowel disease IBS: Irritable bowel syndrome IL: Intestinal lymphangiectasia

LPC: Lymphocytic-plasmacytic colitis LPE: Lymphoplasmacytic enteritis PCR: Polymerase chain reaction PLE: Protein-losing enteropathy

## **ACUTE DIARRHEA**

# **ACUTE ENTERITIS**

#### Etiology

Acute enteritis can be caused by infectious agents, poor diet, abrupt dietary changes, inappropriate foods, additives (e.g., chemicals), and/or parasites. Except for parvovirus, parasites, and obvious dietary indiscretions, the cause is rarely diagnosed because most affected animals spontaneously improve, although supportive therapy may be needed.

#### **Clinical Features**

Diarrhea of unknown cause occurs commonly, especially in puppies and kittens. Signs consist of diarrhea with or without vomiting, dehydration, fever, anorexia, depression, crying, and/or abdominal pain. Very young animals may become hypothermic, hypoglycemic, and stuporous.

# Diagnosis

History and physical and fecal examinations are used to identify possible causes. Fecal flotation (preferably a centrifugal flotation using zinc sulfate flotation solution) and

direct fecal examinations are always indicated because parasites may worsen the problem, even when they are not the main cause. The need for other diagnostic procedures depends on the severity of the illness and on whether the risk of contagion exists. Clinically mild enteritis is usually treated symptomatically, with few diagnostic tests being performed. If the animal is febrile, has hemorrhagic stools, is part of an outbreak of enteritis, or is particularly ill, then additional tests (e.g., complete blood count [CBC] to identify neutropenia, fecal enzyme-linked immunosorbent assay (ELISA) for canine parvovirus, serologic analysis for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), blood glucose to identify hypoglycemia, and serum electrolytes to detect hypokalemia) are indicated. Abdominal radiographs and/or ultrasonography should be evaluated if abdominal pain, masses, obstruction, or foreign body are suspected.

#### **Treatment**

Symptomatic therapy usually suffices. The cause is usually unknown or is a virus for which there is no specific therapy. The goal of symptomatic therapy is reestablishment of fluid, electrolyte, and acid-base homeostasis. Animals with severe dehydration (i.e., ≥8% to 10% as determined by sunken eyes; fast, weak pulse; and marked depression; or a history of significant fluid loss coupled with inadequate fluid intake) should receive intravenous fluids, whereas fluids administered orally or subcutaneously usually suffice for patients that are less severely dehydrated. Potassium supplementation is usually indicated, but bicarbonate is rarely needed. Oral rehydration is sometimes useful in allowing home management of animals, especially when litters of young animals are affected. (See the discussion on fluid, electrolyte, and acid-base therapy in Chapter 30 for details.)

Antidiarrheals are seldom necessary except when excessive fecal losses make maintenance of fluid and electrolyte balance difficult, but they are often requested by clients. Opiates are usually the most effective antidiarrheals. Bismuth subsalicylate (see Table 30-6) is useful in stopping diarrhea in dogs with mild to moderate enteritis. However, absorption of the salicylate may cause nephrotoxicity in some animals (especially when combined with other potentially nephrotoxic drugs), and many dogs dislike the taste. Cats rarely need these medications. (See the discussion on drugs that prolong intestinal transit time in Chapter 30.) If antidiarrheals are needed for more than 2 to 5 days, the animal should be carefully reassessed.

Severe intestinal inflammation often causes vomiting that is difficult to control. Central-acting antiemetics (e.g., dolasteron, ondansetron, maropitant, or prochlorperazine; see Table 30-3) are more likely to be effective than peripheral-acting drugs. The animal should be well hydrated before receiving phenothiazine derivatives, which dilate blood vessels and can produce hypotension.

Although food is typically withheld from animals with severe enteritis to "rest" the intestinal tract, such starvation may be detrimental. Administering even small amounts of food to the intestines helps them recover sooner and prevent breakdown of the mucosal barrier to bacteria. Denying any oral intake is occasionally necessary in animals in which eating causes severe vomiting or explosive diarrhea with substantial fluid loss. However, if feeding does not make the pet's vomiting and diarrhea *much* worse, feeding small amounts of food is probably more beneficial than withholding food. Frequent, small feedings of easily digested, nonirritative foods (e.g., cottage cheese, boiled chicken, potato) is the most common approach. If food must be withheld, it should be reoffered as soon as possible. Some animals with severe enteritis may need parenteral nutrition to establish a positive nitrogen balance.

If the animal is febrile or neutropenic or has systemic inflammatory response syndrome (SIRS) (e.g., septic shock), broad-spectrum systemic antibiotics (e.g.,  $\beta$ -lactam antibiotic plus an aminoglycoside) are indicated (see the discussion of drugs used in gastrointestinal disorders, pp. 409–410). The clinician should observe for hypoglycemia, especially in young animals. Adding dextrose (2.5% to 5%) to the intravenous fluids or administering an intravenous bolus of 50% dextrose (2 to 5 ml/kg) may be necessary to counter hypoglycemia.

If the cause of the diarrhea is unknown, the clinician should assume it to be infectious and disinfect the premises accordingly. Bleach diluted in water (i.e., 1:32) destroys parvovirus and many other infectious agents causing diarrhea. Animals must not be injured by inappropriate contact with such disinfectants. Personnel coming in contact with the animals, cages, and litter should wear protective clothing (e.g., boots, gloves, gowns) that can be discarded or disinfected when leaving the area.

After the enteropathy appears to be clinically resolved, the animal is gradually returned to its normal diet over a 5- to 10-day period. If this change is associated with more diarrhea, then the switch is postponed for another 5 days.

#### Prognosis

The prognosis depends on the animal's condition and can be influenced by its age and other gastrointestinal (GI) problems. Very young or emaciated animals and those with SIRS or substantial intestinal parasite burdens have a more guarded prognosis. Intussusception may occur secondary to acute enteritis, thus worsening the prognosis.

# **ENTEROTOXEMIA**

#### Etiology

The cause is assumed to be bacterial, although causative organisms are almost never isolated.

#### **Clinical Features**

An acute onset of severe, often mucoid-bloody diarrhea that may be associated with vomiting is typical. In severe cases mucus casts of the intestines are expelled, making it appear as if the intestinal mucosa is being lost. In contrast to animals with acute enteritis, these patients usually feel quite ill and may exhibit symptoms of shock early in the course of the disease. CBCs typically reveal a neutrophilic leukocytosis, often with a left shift and sometimes with white blood cell (WBC) toxicity.

# Diagnosis

Exclusion of other causes by history and physical examination coupled with severe WBC changes (e.g., toxicity, left shift) on the CBC allow for presumptive diagnosis. The pet should be checked for intestinal parasites, which may be contributing to the problem. Fecal cultures are rarely useful diagnostically.

#### **Treatment**

These patients typically need aggressive intravenous (IV) fluid therapy plus broad-spectrum antibiotic therapy (e.g., ticarcillin plus clavulinic acid). The serum albumin concentration must be monitored and colloids given if needed. Disseminated intravascular coagulation (DIC) may require plasma and/or heparin therapy.

# **Prognosis**

The prognosis depends on how ill the patient is at presentation.

#### DIETARY-INDUCED DIARRHEA

# **Etiology**

Dietary causes of diarrhea are common, especially in young animals. Poor-quality ingredients (e.g., rancid fat), bacterial enterotoxins or mycotoxins, allergy or intolerance to ingredients, or inability of the animal to digest normal foods are common causes. The latter mechanism revolves around intestinal brush border enzymes that are produced in response to the presence of substrates (e.g., disaccharidases). If the diet is suddenly changed, some animals (especially puppies and kittens) are unable to digest or absorb certain nutrients until the intestinal brush border adapts to the new diet. Other animals may never be able to produce the necessary enzymes (e.g., lactase) to digest certain nutrients (e.g., lactose).

# **Clinical Features**

Diet-induced diarrhea occurs in both dogs and cats. The diarrhea tends to reflect small intestinal dysfunction (i.e., there is usually no fecal blood or mucus) unless there is colonic involvement. The diarrhea usually starts shortly after the new diet is initiated (e.g., 1 to 3 days) and is mild to moderate in severity. Affected animals infrequently have other signs unless parasites or complicating factors are present.

# Diagnosis

History and physical and fecal examinations are used to eliminate other common causes. If diarrhea occurs shortly after a suspected or known dietary change (e.g., after the pet is brought home), a tentative diagnosis of diet-induced disease is reasonable. However, the pet may also be showing the first clinical signs of a recently acquired infection. The animal should always be checked for intestinal parasites because they may contribute to the problem even when they are not the principal cause.

#### **Treatment**

A bland diet (e.g., boiled potato plus boiled skinless chicken) fed in multiple, small feedings (see p. 397) usually causes resolution of the diarrhea in 1 to 3 days. Once the diarrhea resolves, the diet can be gradually changed back to the pet's regular diet.

# **Prognosis**

The prognosis is usually excellent, unless a very young animal with minimal nutritional reserves becomes emaciated, dehydrated, or hypoglycemic.

## INFECTIOUS DIARRHEA

#### **CANINE PARVOVIRAL ENTERITIS**

# Etiology

There are two types of parvoviruses that infect dogs. Canine parvovirus-1 (CPV-1), also known as "minute virus of canines," is a relatively nonpathogenic virus that sometimes is associated with gastroenteritis, pneumonitis, and/or myocarditis in puppies 1 to 3 weeks old. Canine parvovirus-2 (CPV-2) is responsible for classic parvoviral enteritis. CPV-2 usually causes signs 5 to 12 days after the dog is infected via the fecal-oral route, and it preferentially invades and destroys rapidly dividing cells (i.e., bone marrow progenitors, intestinal crypt epithelium).

# **Clinical Features**

The virus has mutated since it was first recognized, and the most recently recognized mutations, CPV-2b, may be more pathogenic in some dogs. CPV-2b and the even more recently identified CPV-2c can also infect cats. The clinical signs depend on the virulence of the virus, the size of the inoculum, the host's defenses, the age of the pup, and the presence of other enteric pathogens (e.g, parasites). Doberman Pinschers, Rottweilers, Pit Bulls, Labrador Retrievers, and German Shepherd dogs may be more susceptible than other breeds. Viral destruction of intestinal crypts may produce villus collapse, diarrhea, vomiting, intestinal bleeding, and subsequent bacterial invasion; however, some animals have mild or even subclinical disease. Many dogs are initially presented because of depression, anorexia, and/or vomiting (which can resemble foreign object ingestion) without diarrhea. Diarrhea is often absent for the first 24 to 48 hours of illness and may not be bloody if and when it does occur. Intestinal protein loss may occur secondary to inflammation, causing hypoalbuminemia. Vomiting is usually prominent and may be severe enough to cause esophagitis. Damage to bone marrow progenitors may produce transient or prolonged neutropenia, making the animal susceptible to serious bacterial infection, especially if a damaged intestinal tract allows bacteria access to the body. Fever and/or septic shock (i.e., systemic inflammatory response syndrome) are common in severely ill dogs but are often absent in less severely affected animals. Puppies that are infected *in utero* or before 8 weeks of age may develop myocarditis.

# **Diagnosis**

Diagnosis is often tentatively made on the basis of history and physical examination findings. Neutropenia is suggestive but is neither sensitive nor specific for canine parvovirus enteritis; salmonellosis or any overwhelming infection can cause similar changes in the CBC. Regardless of whether diarrhea occurs, infected dogs shed large numbers of viral particles in the feces (i.e., >109 particles/g). Therefore ELISA for CPV-2 in the feces is the best diagnostic test. Vaccination with a modified live parvoviral vaccine may cause a weak positive result for 5 to 15 days after vaccination. However, the ELISA results may be negative if the assay is performed early in the clinical course of the disease, and the clinician should not hesitate to repeat this test in dogs that seem likely to have parvoviral enteritis but that initially have negative findings. Shedding decreases rapidly and may be undetectable 10 to 14 days after infection. The real advantage to testing is that either a presumptive diagnosis of parvoviral enteritis is confirmed or other diseases that can mimic parvovirus but require different therapy (e.g., salmonellosis, intussusception) must be considered. Electron microscopic evaluation of feces detects the presence of the virus; however, CPV-1 (which is usually nonpathogenic except perhaps in neonates) is morphologically indistinguishable from CPV-2. If the dog dies, there are typical histologic lesions (i.e., crypt necrosis), and fluorescent antibody and in situ hydridization techniques can establish a definitive diagnosis.

#### **Treatment**

Treatment of canine parvoviral enteritis is fundamentally the same as for any severe, acute, infectious enteritis (see p. 441). Fluid and electrolyte therapy is crucial and is typically combined with antibiotics (Box 33-1). Most dogs will live if they can be supported long enough. However, very young puppies, dogs in severe septic shock, and certain breeds seem to have more problems and may have a more guarded prognosis. Mistakes include inadequate fluid therapy (common), overzealous fluid administration (especially in dogs with severe hypoproteinemia), failure to administer glucose to hypoglycemic patients, failure to supplement adequate potassium, unrecognized sepsis, and unsuspected concurrent GI disease (e.g., parasites, intussusception).

If the serum albumin concentration is less than 2.0 g/dl, it is advantageous to administer plasma. Colloids such as hetastarch may be substituted for plasma, but they do not contain antibodies that might be beneficial. Antibiotic therapy is needed if evidence of infection (i.e., fever, septic shock) exists or there is risk of infection (i.e., severe neutropenia). If the animal is neutropenic but afebrile, the admin-



BOX 33-1

#### General Guidelines for Treatment of Canine Parvoviral Enteritis\*

#### Fluids†‡

Administer balanced electrolyte solution with 30-40 mEq potassium chloride/L.

Calculate maintanence requirements (i.e., 66 ml/kg/day with dogs <5 kg needing up to 80 ml/kg/day).

Estimate deficit (better to slightly overestimate rather than underestimate the deficit).

Dogs with very mild cases may receive subcutaneous fluids (intravenous fluids still preferred), but watch for sudden worsening of the disease.

Dogs with moderate to severe cases should receive fluids via intravenous or intramedullary route.

Add 2.5%-5% dextrose to the intravenous fluids if hypoglycemia or systemic inflammatory response syndrome is present or is a risk.

Administer plasma or hetastarch if dog has serum albumin ≤2.0 g/dl.

Plasma: 6-10 ml/kg over 4 hours; repeat until the desired serum albumin concentration is attained

Hetastarch: 10-20 ml/kg

#### Antibiotics†

Administer to febrile or severely neutropenic dogs.

Prophylactic antibiotics for nonfebrile neutropenic patients (e.g., cefazolin).

Broad-spectrum antibiotics for febrile, neutropenic patients (e.g., ticarcillin/clavulinic acid plus amikacin).

#### **Antiemetics**

Given if needed:

Serotonin receptor antagonists

- Dolasetron
- Ondansetron

Maropitant (minimal clinical experience at the time of this writing)

Metoclopramide (constant rate infusion is more effective than intermittent bolusing)

H<sub>2</sub>-receptor antagonists (for antidyspepsia effects)

• Famotidine

## **Anthelmintics**

Pyrantel (should be given after feeding)

Ivermectin (this drug is absorbed in the oral mucous membranes; do not give to breeds that are likely to have adverse effects, such as Collies, Old English Sheepdogs, etc.)

#### **Dogs With Secondary Esophagitis**

If regurgitation occurs in addition to vomiting, administer: H<sub>2</sub>-receptor antagonists (injectable) Sucralfate (Carafate) slurry

# Special Nutritional Therapy

Try to feed dog small amounts as soon as feeding does not cause major exacerbation in vomiting.

"Microenteral" nutrition (slow drip of enteral diet administered via nasoesophageal tube) if dog refuses to eat and administration does not make vomiting worse

Administer parenteral nutrition if prolonged anorexia occurs

Peripheral parenteral nutrition is more convenient than total parenteral nutrition

#### **Monitor Physical Status**

Physical examination (1-3 times per day depending on severity of signs)

Body weight (1-2 times per day to assess changes in hydration status)

Potassium (every 1-2 days depending on severity of vomiting/diarrhea)

Serum protein (every 1-2 days depending on severity of signs)

Glucose (every 4-12 hours in dogs that have systemic inflammatory response syndrome or were initially hypoglycemic)

Packed cell volume (every 1-2 days)

White blood cell count: either actual count or estimated from a slide (every 1-2 days in febrile animals)

# Controversial Therapies

Recominant feline IFN-ώ: One report suggests that this therapy was useful.

Tamiflu (anecdotally beneficial if used early in the course of the disease)

Flunixin Meglumine: Sometimes used for patients with systemic inflammatory response syndrome, but perforation and bleeding are significant risks.

istration of a first-generation cephalosporin is reasonable. If the animal is in septic shock (i.e., systemic inflammatory response syndrome), then an antibiotic combination with a broad aerobic and anerobic spectrum is recommended (e.g., ticarcillin or ampicillin plus amikacin or enrofloxacin). Aminoglycosides should not be administered until the patient is rehydrated and renal perfusion is re-established. Caution should be used when administering enrofloxacin to young, large-breed dogs lest cartilage damage occur. Severe vomiting complicates therapy and may require administration of

<sup>\*</sup> The same guidelines generally apply to dogs with other causes of acute enteritis/gastritis.

<sup>†</sup> Usually the first considerations when an animal is presented.

<sup>‡</sup>A history of decreased intake plus increased loss such as vomiting and/or diarrhea confirms dehydration, regardless of whether dog appears to be dehydrated.

dolasetron, ondansetron, or maropitant (see Table 30-3). If esophagitis occurs,  $H_2$ -receptor antagonists may be useful (see Table 30-4). Human granulocyte colony–stimulating factor (G-CSF) (5 µg/kg q24h) to increase neutrophil numbers and tamiflu (oseltamivir phosphate) (2 mg/kg q12-24h) to combat the virus have been advocated; however, there is no evidence that either substantively benefits the patient. Flunixin meglamine has been suggested for patients in septic shock, but care must be taken lest iatrogenic ulceration/perforation occurs. Recombinant feline IFN- $\dot{\omega}$  (2.5 × 10<sup>6</sup> units per kg) has been suggested to improve the chance of survival.

If possible, feeding small amounts of liquid diet via a nasoesophageal (NE) tube seems to help the intestines to heal more rapidly. A bland diet may be fed once vomiting has ceased for 18 to 24 hours. Parenteral nutrition can be life saving for patients that are persistently unable to hold down oral food. It can be equally critical for patients unable to accept any enteral nutrition. Partial parenteral nutrition is easier and less expensive than total parenteral nutrition. The dog should be kept away from other susceptible animals for 2 to 4 weeks after discharge, and the owner should be conscientious about the disposal of feces. Vaccination of other dogs in the household should be considered.

When trying to prevent the spread of parvoviral enteritis, the clinician must remember that (1) parvovirus persists for long periods of time (i.e., months) in the environment, making it difficult to prevent exposure; (2) asymptomatic dogs may shed virulent CPV-2; (3) maternal immunity sufficient to inactivate vaccine virus may be present in some puppies; and (4) dilute bleach (1:32) is one of the few readily available disinfectants that kills the virus, but it can take 10 minutes to achieve effectiveness.

Vaccination of pups should generally commence at 6 to 8 weeks of age. The antigen density and immunogenicity of the vaccine as well as the amount of antibody transferred from the bitch determine when the pup can be successfully immunized. Inactivated vaccines generally are not as successful as attenuated vaccines, and giving a series of these vaccinations seems best. Attenuated vaccines are generally more successful in producing a long-lasting immunity. When the immune status of the pup is unknown, administering an attenuated vaccine at 6, 9, and 12 weeks of age is usually successful. If vaccination before 5 to 6 weeks of age is deemed necessary, an inactivated vaccine is safer. Regardless of the vaccine used, it appears that there is typically a 2- to 3-week window during which the pup is susceptible to parvovirus infection and yet cannot be successfully immunized. Annual revaccination is generally recommended for parvovirus, although it is possible that vaccination every 3 years may be sufficient after the initial series as a puppy. Adults that were previously not vaccinated usually receive two doses 2 to 4 weeks apart. There is no strong evidence that parvoviral vaccination should be given separately from modified-live canine distemper vaccinations. However, modified-live vaccinations should not be administered to patients younger

than 5 weeks of age or those suspected of incubating or being affected with distemper.

If parvoviral enteritis develops in one dog in a multipledog household, it is reasonable to administer booster vaccinations to the other dogs, preferably using an inactivated vaccine in case they are incubating the infection at the time of immunization. If the client is bringing a puppy into a house with a dog that has recently had parvoviral enteritis, the puppy should be kept elsewhere until it has received its immunizations.

# **Prognosis**

Dogs treated in a timely fashion with proper therapy typically live, especially if they survive the first 4 days of clinical signs. The possible sequela of intussusception may cause persistent diarrhea in pups recovering from the viral infection. Dogs that have recovered from CPV-2 enteritis develop long-lived immunity that may be lifelong. Whether immunization against CPV-1 will be needed is unknown.

#### FELINE PARVOVIRAL ENTERITIS

# **Etiology**

Feline parvoviral enteritis (feline distemper, feline panleukopenia) is caused by feline panleukopenia virus (FPV), which is distinct from CVP-2b. However, CPV-2a, CPV-2b, and CPV-2c can infect cats and cause disease.

# **Clinical Features**

Many infected cats never show clinical signs of disease. Signs in affected cats are usually similar to those described for dogs with parvoviral enteritis. Kittens affected *in utero* may develop cerebellar hypoplasia.

## Diagnosis

Diagnosis is similar to that described for canine parvovirus. The ELISA test for fecal CPV is also a good test for feline parvovirus. However, it is important to note that the test may be positive for only 1 to 2 days after infection, and by the time the cat is clinically ill, this test may not be able to detect viral shedding in the feces.

#### **Treatment**

Cats with parvoviral infection are treated much in the same way as described for dogs with the disease. A major difference between dogs and cats centers on immunization: Parvoviral vaccine seems to engender a better protective response in cats than in dogs. However, kittens younger than 4 weeks of age should not be vaccinated with modified live virus vaccines lest cerebellar hypoplasia occur. Also, the vaccine cannot be administered orally, but intranasal adminstration is effective.

# **Prognosis**

As with dogs, many affected cats live if overwhelming sepsis is prevented and they can be supported long enough.

## **CANINE CORONAVIRAL ENTERITIS**

# Etiology

Canine coronaviral enteritis occurs when coronavirus invades and destroys mature cells on the intestinal villi. Because intestinal crypts remain intact, villi regenerate more quickly in dogs with coronaviral enteritis than in dogs with parvoviral enteritis; bone marrow cells are not affected.

#### **Clinical Features**

Coronaviral enteritis is typically less severe than classic parvoviral enteritis and rarely causes hemorrhagic diarrhea, septicemia, or death. Dogs of any age may be infected. Signs usually last less than 1 to  $1^{1}/_{2}$  weeks, and small or very young dogs may die as a result of dehydration or electrolyte abnormalities if they are not properly treated. Dual infection with parvovirus may produce a high incidence of morbidity and mortality.

# Diagnosis

Because canine coronaviral enteritis is usually much less severe than many other enteritides, it is seldom definitively diagnosed. Most dogs are treated symptomatically for acute enteritis until they improve. Electron microscopic examination of feces obtained early in the course of the disease can be diagnostic. However, the virus is fragile and easily disrupted by inappropriate handling of the feces. A history of contagion and elimination of other causes are reasons to suspect canine coronaviral enteritis.

#### Treatment

Fluid therapy, motility modifiers (see Chapter 30), and time should resolve most cases of coronaviral enteritis. Symptomatic therapy (see p. 441) is usually successful except, perhaps, for very young animals. A vaccination is available but of uncertain value except, perhaps, in animals at high risk of infection (e.g., those in infected kennels or dog shows).

# **Prognosis**

The prognosis for recovery is usually good.

#### FELINE CORONAVIRAL ENTERITIS

Infections in adults are often asymptomatic, whereas kittens may have mild, transient diarrhea and fever. Deaths are rare, and the prognosis for recovery is excellent. This disease is important because (1) affected animals seroconvert and may become positive on feline infectious peritonitis serologic analysis and (2) mutation by the feline coronavirus may be the cause of feline infectious peritonitis.

# FELINE LEUKEMIA VIRUS-ASSOCIATED PANLEUKOPENIA (MYELOBLASTOPENIA)

# **Etiology**

FeLV-associated panleukopenia (myeloblastopenia) may actually be caused by co-infection with FeLV and FPV. The intestinal lesion histologically resembles that produced

by feline parvovirus. The bone marrow and lymph nodes are not consistently affected as they are in cats with parvoviral enteritis.

#### **Clinical Features**

Chronic weight loss, vomiting, and diarrhea are common. The diarrhea often has characteristics of large bowel disease. Anemia is common.

# Diagnosis

Finding FeLV infection in a cat with chronic diarrhea is suggestive. Cats are typically neutropenic. Histologic lesions of FPV in a cat with FeLV should be definitive.

#### **Treatment**

Symptomatic therapy (fluid/electrolyte therapy, antibiotics, antiemetics, and/or highly digestible bland diets as needed) and elimination of other problems that compromise the intestines (e.g., parasites, poor diet) may be beneficial.

# **Prognosis**

This disease has a poor prognosis because of other FeLV-related complications.

# FELINE IMMUNODEFICIENCY VIRUS-ASSOCIATED DIARRHEA

# **Etiology**

FIV may be associated with severe, purulent colitis. The pathogenesis is unclear and may involve multiple mechanisms.

#### **Clinical Features**

Severe large bowel disease is common and can occasionally result in colonic rupture. These animals generally appear ill, whereas most cats with chronic large bowel disease caused by inflammatory bowel disease (IBD) or dietary intolerance seemingly feel fine.

# Diagnosis

Detection of antibodies to FIV plus severe, purulent colitis allows presumptive diagnosis.

#### Treatment

Therapy is supportive (e.g., fluids/electrolytes, antiemetics, antibiotics, and/or highly digestible bland diets as needed).

#### **Prognosis**

The long-term prognosis is very poor, although some cats can be maintained for months.

# SALMON POISONING/ELOKOMIN FLUKE FEVER

# Etiology

Salmon poisoning is caused by *Neorickettsia helminthoeca*. Dogs are infected when they eat fish (primarily salmon) infected with a fluke (*Nanophyetus salmincola*) that carries the rickettsia. The rickettsia spreads to the intestines and

most lymph nodes, causing inflammation. This disease is principally found in the Pacific northwestern United States because the snail intermediate host (Oxytrema silicula) for N. salmincola lives there. The Elokomin fluke fever agent may be a strain of N. helminthoeca.

#### **Clinical Features**

Dogs, not cats, are affected. The severity of signs varies and typically consists of initial fever that eventually falls and becomes subnormal. Fever is followed by anorexia and weight loss, which may also involve vomiting and/or diarrhea. The diarrhea is typically small bowel but may become bloody.

# Diagnosis

Presumptive diagnosis is usually based on the animal's habitat plus a history of recent consumption of raw fish or exposure to streams or lakes. Finding *Nanophyetus* spp. ova (operculated trematode ova) in the stool is very suggestive, and finding rickettsia in fine-needle aspirates of enlarged lymph nodes is confirmatory.

#### **Treatment**

Treatment consists of symptomatic control of dehydration, vomiting, and diarrhea and elimination of the rickettsia and fluke. Tetracycline, oxytetracycline, doxycycline, or chloramphenicol (see Chapter 93) eliminates the rickettsia. The fluke is killed with praziquantel (see Table 30-7).

# **Prognosis**

The prognosis depends on the clinical severity at the time of diagnosis. Most dogs respond favorably to tetracyclines and supportive therapy. The key to success is awareness of the disease. Untreated salmon poisoning has a poor prognosis.

# BACTERIAL DISEASES: COMMON THEMES

The following bacterial diseases all have certain aspects in common. First, all of these bacteria may be found in feces from clinically normal dogs and cats. Simply growing the bacteria or finding toxin produced by the bacteria in the patient's feces are insufficient by themselves to definitively diagnose intestinal disease as being caused by this particular organism. Diagnosis can be made only by finding clinical disease consistent with a particular organism, evidence of the organism or its toxin, eliminating other causes of the clinical signs, and seeing the expected response to appropriate therapy. If the clinician undertakes culture, it is crucial to call the laboratory ahead of time, tell staff members what is being sought through culture, and follow their instructions regarding submission of the sample.

The problems with making a diagnosis using the previously mentioned criteria are obvious, and caution is warranted before making definitive statements regarding cause and effect. In many cases, the best chance of making a definitive diagnosis involves following the guidelines described

and using molecular techniques on isolates to demonstrate toxin production.

#### **CAMPYLOBACTERIOSIS**

# Etiology

There are several species of Campylobacter. Campylobacter jejuni is the species routinely associated with GI disease, although Campylobacter upsaliensis has been implicated. These organisms prefer high temperatures (i.e., 39° to 41° C); hence poultry is probably a reservoir. These organisms are found in the intestinal tract of healthy dogs and cats.

#### **Clinical Features**

Symptomatic campylobacteriosis is principally diagnosed in animals younger than 6 months old living in crowded conditions (e.g., kennels, humane shelters) or as a nosocomial infection. Mucoid diarrhea (with or without blood), anorexia, and/or fever are the primary signs. Campylobacteriosis tends to be self-limiting in dogs, cats, and people; however, it occasionally causes chronic diarrhea.

# Diagnosis

Occasionally, classic *Campylobacter* forms may be found during cytologic examination of a fecal smear (i.e., "commas," "seagull wings"). This cytology is thought to be specific but of uncertain sensitivity. Polymerase chain reaction (PCR) analysis of feces is available.

# **Treatment**

If campylobacteriosis is suspected, erythromycin (11 to 15 mg/kg administered orally q8h) or neomycin (20 mg/kg administered orally q12h) is usually effective.  $\beta$ -lactam antibiotics (i.e., penicillins, first-generation cephalosporins) are often ineffective. The length of treatment necessary for cure has not been firmly established. The animal should be treated for at least 1 to 3 days beyond resolution of clinical signs; however, antibiotic therapy may not eradicate the bacteria, and reinfection is likely in kennel conditions. Chronic infections may require prolonged therapy (e.g., weeks).

This bacterium is potentially transmissible to people, and there are cases in which there is convincing evidence of transmission from pets to people. Infected dogs and cats should be isolated, and individuals working with the animal or its environment or wastes should wear protective clothing and wash with disinfectants.

#### **Prognosis**

With appropriate antibiotic therapy, the prognosis for recovery is good.

# **SALMONELLOSIS**

# **Etiology**

There are numerous Salmonella serotypes that may cause disease; Salmonella typhimurium is one of the serovars that is more commonly associated with disease. The bacteria may originate from animals shedding the organism (e.g., infected

dogs and cats) or from contaminated foods (especially poultry and eggs).

# **Clinical Features**

Salmonella spp. may produce acute or chronic diarrhea, septicemia, and/or sudden death, especially in very young or geriatric animals. Salmonellosis in young animals can produce a syndrome that closely mimics parvoviral enteritis (including severe neutropenia), which is one reason that ELISA testing for parvovirus is useful. The fact that salmonellosis occasionally develops during or after canine parvoviral enteritis makes the situation more confusing.

# **Diagnosis**

Culture of *Salmonella* spp. from normally sterile areas (e.g, blood) confirms that it is causing disease. Identification by PCR can be a sensitive method of diagnosis.

#### **Treatment**

Treatment depends on the clinical signs. Animals with diarrhea as the sole sign may need only supportive fluid therapy (including plasma in hypoalbuminemic patients). Nonsteroidal drugs (to lessen intestinal secretion) and lactulose have been used in such patients. Antibiotics are of dubious value and might promote a carrier state. Septicemic (i.e., febrile) animals should receive supportive therapy and parenteral antibiotics as determined by susceptibility testing, but quinolones, potentiated sulfa drugs, amoxicillin, and chloramphenicol are often good initial choices (see the discussion of drugs used in gastrointestinal disorders, pp. 409–410). Aggressive plasma therapy might be beneficial in such patients.

Infected animals are public health risks (especially for infants and older adults) and should be isolated from other animals, at least until they are asymptomatic. Even when signs disappear, reculturing of feces is reasonable to ensure that shedding has stopped. Individuals in contact with the animal, its environment, and its waste should wear protective clothing and wash with disinfectants such as phenolic compounds and bleach (1:32 dilution).

# **Prognosis**

The prognosis is usually good in animals with only diarrhea but guarded in septicemic dogs and cats.

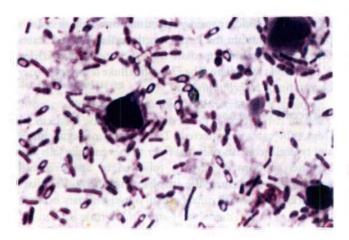
# **CLOSTRIDIAL DISEASES**

# **Etiology**

Clostridium perfringens and Clostridium difficile can be found in clinically normal dogs but appear to cause diarrhea in some. For *C. perfringens* to produce disease, the bacteria must possess the ability to produce toxin, and environmental conditions must be such that toxin is produced.

# **Clinical Features**

C. perfringens apparently may produce an acute, bloody, selflimiting nosocomial diarrhea; an acute, potentially fatal



IG 33-1

Photomicrograph of air-dried canine feces stained with Diff-Quik. Numerous spores are seen as clear vacuoles in darkly stained rods. (Magnification ×1000.)

hemorrhagic diarrhea; or a chronic large bowel or small bowel (or both) diarrhea (with or without blood or mucus). This clostridial disease is primarily recognized in dogs. Disease associated with *C. difficile* is poorly characterized in small animals but may include large bowel diarrhea, especially after antibiotic therapy.

# **Diagnosis**

In particular, finding spore-forming bacteria on fecal smears (Fig. 33-1) is not diagnostic. Commercially available toxin assays for *C. difficile* toxin have not been validated for the dog or cat, and results do not necessarily correlate with the patient's clinical condition. Determining that the patient has large bowel diarrhea without weight loss or hypoalbuminemia, elimination of other causes, and resolution of signs when treated appropriately (see next paragraph) is typically the basis for presumptive diagnosis.

#### **Treatment**

If *C. perfringens* disease is suspected, the animal may be treated with tylosin or amoxicillin, and response is expected shortly. Some animals are cured after a 1- to 3-week course of therapy. However, antibiotic treatment does not necessarily eliminate the bacteria, and some dogs need indefinite therapy. Tylosin (20 to 80 mg/kg/day, divided, q12h) or amoxicillin (22 mg/kg q12h) seems to be effective and yet has minimal adverse effects in these animals. Some animals can eventually be maintained with once daily or every-otherday antibiotic therapy. Some dogs with chronic diarrhea seemingly caused by *C. perfringens* respond well to fibersupplemented diets. Metronidazole is not as consistently effective as tylosin or amoxicillin. The prognosis is good, and there is no obvious public health risk, although there is anecdotal evidence of transmission between people and dogs.

If disease caused by *C. difficile* is suspected, supportive fluid and electrolyte therapy may be necessary depending on the severity of signs. Metronidazole should be effective in killing this bacterium, but one must be sure to use a sufficiently

high dose to achieve adequate metronidazole concentrations in the feces. Vancomycin is often used to treat people with this disease but has not generally been necessary in dogs or cats.

# **Prognosis**

The prognosis is excellent in dogs with diarrhea caused by *C. perfringens* but uncertain for those cases caused by *C. difficile*.

# MISCELLANEOUS BACTERIA

# **Etiology**

Yersinia enterocolitica, Aeromonas hydrophila, and Plesiomonas shigelloides may cause acute or chronic enterocolitis in dogs and/or cats as well as in people. However, these bacteria (especially the latter two) are uncommonly diagnosed in the United States. Y. enterocolitica is primarily found in cold environments and in pigs, which may serve as a reservoir. It is also a cause of food poisoning because of its ability to grow in cold temperatures. Enterohemorrhagic Escherichia coli (EHEC) may seemingly be associated with canine and feline diarrhea, although it does not appear to be especially common.

# **Clinical Features**

Small bowel diarrhea may be caused by any of these bacteria. Yersiniosis usually affects the colon and produces chronic large bowel diarrhea. Affected people report substantial abdominal pain.

# Diagnosis

Animals with persistent colitis, especially those that are in contact with pigs, may reasonably be cultured for *Y. enterocolitica*.

#### **Treatment**

Therapy is supportive. The affected animal should be isolated from other animals. People in contact with the animal and/or its environment and wastes should wear protective clothing and clean themselves with disinfectants. Although antibiotics intuitively seem indicated, their use has not shortened clinical disease caused by EHEC. Nonetheless, appropriate antibiotics as determined by culture and sensitivity are used (e.g., *Y. enterocolitica* is often sensitive to tetracyclines). The preferred length of antibiotic therapy has not been established, but treatment should probably be continued for 1 to 3 days beyond clinical remission.

# **Prognosis**

The prognosis is uncertain but seems to be good if the bacteria can be identified by culture and the infection treated appropriately.

# **HISTOPLASMOSIS**

# Etiology

Caused by Histoplasma capsulatum, histoplasmosis is a mycotic infection that may affect the GI, respiratory, and/or

reticuloendothelial systems, as well as the bones and eyes. Principally found in animals from the Mississippi and Ohio River valleys, it occurs in other areas as well.

# **Clinical Features**

Alimentary tract involvement is primarily found in dogs; diarrhea (with or without blood or mucus) and weight loss are common signs. The lungs, liver, spleen, lymph nodes, bone marrow, bones, and/or eyes may also be affected. Symptomatic alimentary involvement is much less common in cats, in which respiratory dysfunction (e.g., dyspnea, cough), fever, and/or weight loss are more common.

In GI histoplasmosis, the colon is usually the most severely affected segment. Diffuse, severe, granulomatous, ulcerative mucosal disease can produce bloody stool, intestinal protein loss, intermittent fever, and/or weight loss. Small intestinal involvement occasionally occurs. The disease may smolder for long periods of time, causing mild to moderate, nonprogressive signs. Occasionally, histoplasmosis causes focal colonic granulomas or is present in grossly normal-appearing colonic mucosa.

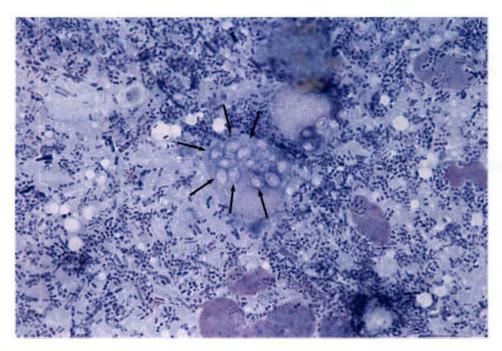
# Diagnosis

Diagnosis requires finding the yeast (Fig. 33-2), although a recent test for antigen present in urine is being evaluated. Dogs from endemic areas with chronic large bowel diarrhea are especially suspect. Protein-losing enteropathy is common in dogs with severe histoplasmosis, and hypoalbuminemia in dogs with large bowel disease is suggestive of the disease, regardless of the location.

Rectal examination sometimes reveals thickened rectal folds, which can easily be scraped with a dull curette or syringe cap to obtain material for cytologic preparations. Evaluation of colonic biopsy specimens is usually diagnostic, but special stains may be necessary. Mesenteric lymph node samples or repeated colonic biopsy is rarely required. Fundic examination occasionally reveals active chorioretinitis. Abdominal radiographs might reveal hepatosplenomegaly, and thoracic radiographs sometimes demonstrate pulmonary involvement (e.g., miliary interstitial involvement and/or hilar lymphadenopathy). Cytologic evaluation of hepatic or splenic aspirates may be diagnostic. The CBC rarely reveals yeasts in circulating WBCs. Thrombocytopenia may occur. Cytologic examination of bone marrow or of buffy coat smears may reveal the organism. Serologic tests and fecal culture for the yeast are unreliable.

#### **Treatment**

It is crucial to look for histoplasmosis before beginning empiric corticosteroid therapy for suspected canine colonic IBD. Corticosteroid therapy lessens host defenses and may allow a previously treatable case to rapidly progress and kill the animal. Itraconazole by itself or preceded by amphotericin B is often effective (see Chapter 98). Treatment should be continued long enough (i.e., at least 4 to 6 months) to lessen chances for relapse.



#### FIG 33-2

Cytologic preparation of a colonic mucosal scraping demonstrating *Histoplasma capsulatum*. Note the macrophage with numerous yeasts in the cytoplasm *(arrows)*. (Wright-Giemsa stain; magnification ×400.) (From Allen D, editor: *Small animal medicine*, Philadelphia, 1991, JB Lippincott.)

#### **Prognosis**

Many dogs can be cured if treated relatively early. Multiple organ system involvement worsens the prognosis, as does central nervous system (CNS) involvement.

#### **PROTOTHECOSIS**

# **Etiology**

Prototheca zopfii is an alga that invades tissue. It appears to be acquired from the environment, and some type of deficiency in the host's immune system might be needed for the organism to produce disease.

# **Clinical Features**

Affecting dogs and occasionally cats, protothecosis principally involves the skin, colon, and eyes but may disseminate throughout the body. Collies may be overrepresented. Colonic involvement causes bloody stools and other signs of colitis, much like histoplasmosis. Protothecosis is much less common than histoplasmosis, and the GI form primarily affects dogs.

# **Diagnosis**

Diagnosis requires demonstrating the organism (Fig. 33-3).

## **Treatment**

Most drugs work inconsistently. High doses of amphotericin B (administered via liposomes) might be useful.

# **Prognosis**

The prognosis for disseminated disease is poor because no treatment consistently works.

# **ALIMENTARY TRACT PARASITES**

## WHIPWORMS

#### Etiology

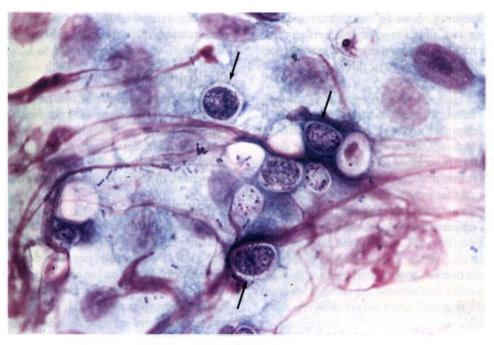
Trichuris vulpis is principally found in the eastern United States. Animals acquire the infection by ingesting ova; the adults burrow into the colonic and cecal mucosa and may cause inflammation, bleeding, and intestinal protein loss.

## **Clinical Features**

Dogs and rarely cats acquire whipworms, which produce a wide spectrum of mild to severe colonic disease that can include hematochezia and protein-losing enteropathy. Severe trichuriasis may cause severe hyponatremia and hyperkalemia, mimicking hypoadrenocorticism. Marked hyponatremia might be responsible for CNS signs (e.g., seizures). Whipworms generally do not affect cats as severely as dogs.

# **Diagnosis**

T. vulpis should always be sought in dogs with bloody stools or other colonic disease. Diagnosis is made through finding ova (Fig. 33-4) in the feces or seeing the adults at endoscopic



**FIG 33-3**Cytologic preparation of a colonic mucosal scraping demonstrating *Prototheca* spp. Note the bean-shaped structures that have a granular internal structure and appear to have a halo *(arrows)*. (Wright-Giemsa stain; magnification ×1000.) (Courtesy Dr. Alice Wolf, Texas A & M University.)



Photomicrograph of a fecal flotation analysis from a dog, demonstrating characteristic ova from whipworms (W), Toxocara canis (T), and Isospora spp. (I). The remaining ova are those of an unusual tapeworm, Spirometra sp. (Magnification ×250.) (Courtesy Dr. Tom

Craig, Texas A & M University.)

evaluation. However, these ova are relatively dense and float only in properly prepared flotation solutions. Furthermore, ova are shed intermittently and sometimes can be found only if multiple fecal examinations are performed.

#### **Treatment**

Because of the potential difficulty in diagnosing *T. vulpis*, it is reasonable to empirically treat dogs with chronic large bowel disease with fenbendazole or other appropriate drugs (see Table 30-7) before proceeding to endoscopy. If a dog is treated for whipworms, it should be treated again in 3 months to kill worms that were not in the intestinal lumen at the time of the first treatment. The ova persist in the environment for long periods.

# **Prognosis**

The prognosis for recovery is good.

## **ROUNDWORMS**

# Etiology

Roundworms are common in dogs (*Toxocara canis* and *Toxascaris leonina*) and cats (*Toxocara cati* and *Toxascaris leonina*). Dogs and cats can obtain roundworms from ingesting the ova (either directly or via paratenic hosts). *T. canis* is often obtained transplacentally from the mother; *T. cati* may use transmammary passage, and *T. leonina* can use intermediate hosts. Tissue migration of immature forms can cause hepatic fibrosis and significant pulmonary lesions. Adult roundworms live in the small intestinal lumen

and migrate against the flow of ingesta. They can cause inflammatory infiltrates (e.g., eosinophils) in the wall of the intestine.

#### **Clinical Features**

Roundworms may cause or contribute to diarrhea, stunted growth, a poor haircoat, and poor weight gain, especially in young animals. Runts with "potbellies" suggest severe roundworm infection. Sometimes, roundworms gain access to the stomach, in which case they may be vomited. If parasites are numerous, they may obstruct the intestines or bile duct.

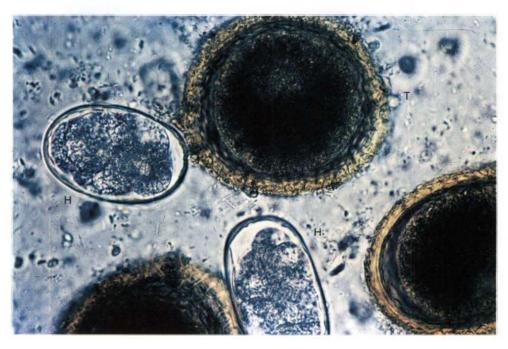
# **Diagnosis**

Diagnosis is easy because ova are produced in large numbers and are readily found by fecal flotation (Fig. 33-5; see also Fig. 33-4). Occasionally, neonates develop clinical signs of roundworm infestation but ova cannot be found in the feces. Transplacental migration results in large worm burdens, causing signs in these animals before the parasites mature and produce ova.

#### **Treatment**

Various anthelmintics are effective (see Table 30-7), but pyrantel is especially safe for young dogs and cats, particularly those with diarrhea. Affected animals should be retreated at 2- to 3-week intervals to kill roundworms that were initially in tissues but migrated into the intestinal lumen since the last treatment.

High-dose fenbendazole therapy (i.e., 50 mg/kg/day from day 40 of gestation until 2 weeks postpartum) has been sug-



Photomicrograph of a fecal flotation analysis from a dog demonstrating characteristic ova from hookworms (H) and Toxocara canis (T). (Magnification ×400.) (Courtesy Dr. Tom Craig, Texas A & M University.)

gested to reduce the somatic roundworm burden in bitches and lessen transplacental transmission to puppies. Newborn puppies can be treated with fenbendazole (100 mg/kg for 3 days), which kills more than 90% of prenatal larvae. This treatment can be repeated 2 to 3 weeks later. Preweaning puppies should be treated at 2, 4, 6, and 8 weeks of age to lessen contamination of the environment because *T. canis* and *T. cati* pose a human health risk (i.e., visceral and ocular larval migrans). Preweaning kittens should be treated at 6, 8, and 10 weeks of age.

# **Prognosis**

The prognosis for recovery is good unless the animal is already severely stunted when treated, in which case it may never attain its anticipated body size.

#### **HOOKWORMS**

# Etiology

Ancylostoma spp. and Uncinaria spp. are more common in dogs than in cats. Infestation is usually via ingestion of the ova or through transcolostral transmission; freshly hatched larvae may also penetrate the skin. The adults live in the small intestinal lumen, where they attach to the mucosa. Plugs of intestinal mucosa and/or blood is ingested, depending on the worm species. In severe infestations hookworms may be found in the colon.

#### **Clinical Features**

Dogs are more severely affected than cats. Young animals may have life-threatening blood loss or iron-deficiency anemia, melena, frank fecal blood, diarrhea, and/or failure to thrive. Older dogs rarely have disease solely caused by hookworms unless they harbor a massive infestation, but these worms may still contribute to disease caused by other intestinal problems.

#### Diagnosis

Finding ova in the feces is diagnostic (see Fig. 33-5) and easy because hookworms are prolific egg producers. However, 5- to 10-day-old puppies may be exsanguinated by transcolostrally obtained hookworms before ova appear in the feces. Such prepatent infections rarely occur in older animals that have received a sudden, massive exposure. Diagnosis is suggested by signalment and clinical signs in these animals. Iron deficiency anemia in a puppy or kitten free of fleas is highly suggestive of hookworm infestation.

#### **Treatment**

Various anthelmintics are effective (see Table 30-7). Treatment should be repeated in approximately 3 weeks to kill parasites entering the intestinal lumen from the tissues. In anemic puppies and kittens, blood transfusions may be life saving.

Application of moxidectin to pregnant bitches on day 55 of pregnancy reduces transcolostral transmission to puppies. Hookworms are a potential human health hazard (i.e., cuta-

neous larval migrans). Use of heartworm preventives containing pyrantel or milbemycin helps to minimize hookworm infestations.

# **Prognosis**

The prognosis is good in mature dogs and cats but guarded in severely anemic puppies and kittens. If the puppies or kittens are severely stunted in their growth, they may never attain their anticipated body size.

#### **TAPEWORMS**

# Etiology

Several tapeworms infect dogs and cats, the most common being *Dipylidium caninum*. Tapeworms usually have an indirect life cycle; the dog or cat is infected when it eats an infected intermediate host. Fleas and lice are intermediate hosts for *D. caninum*, whereas wild animals (e.g., rabbits) are intermediate hosts for some *Taenia* spp.

#### **Clinical Features**

Aesthetically offensive, tapeworms are rarely pathogenic in small animals, although *Mesocestoides* spp. can reproduce in the host and cause disease (e.g., abdominal effusion). The most common sign in infested dogs and cats is anal irritation associated with shed segments "crawling" on the area. Typically, the owner sees motile tapeworm segments on the feces and requests treatment. Occasionally, a segment enters an anal sac and causes inflammation. Very rarely, large numbers of tapeworms cause intestinal obstruction.

# Diagnosis

Taenia spp. and especially *D. caninum* eggs are typically confined in segments not detected by routine fecal flotations. *Echinococcus* spp. and some *Taenia* spp. ova may be found in the feces. Tapeworms are usually diagnosed when the owner reports tapeworm segments (e.g., "rice grains") on feces or the perineal area.

#### **Treatment**

Praziquantel and episprantel are effective against all species of tapeworms (see Table 30-7). Prevention of tapeworms involves controlling the intermediate hosts (i.e., fleas and lice for *D. caninum*). *Echinococcus* spp. are a human health hazard.

#### **STRONGYLOIDIASIS**

# Etiology

Strongyloides stercoralis principally affects puppies, especially those in crowded conditions. These parasites produce motile larvae that penetrate unbroken skin or mucosa; thus the animal may be infested from its own feces even before the larvae are evacuated from the colon. In this manner, animals can quickly acquire large parasitic burdens. Most animals are infested after being exposed to fresh feces containing the

motile larvae. Humane shelters and pet stores are likely sources for infestation.

# **Clinical Features**

Infested animals usually have mucoid or hemorrhagic diarrhea and are systemically ill (e.g., lethargy). Respiratory signs (i.e., verminous pneumonia) occur if parasites penetrate the lungs.

# **Diagnosis**

S. stercoralis is diagnosed by finding the larvae in fresh feces, either by direct fecal examination or by Baermann sedimentation. Strongyloides larvae must be differentiated from Oslerus spp. larvae. The feces must be fresh because old feces may contain hatched hookworm larvae, which resemble those of Strongyloides spp.

#### **Treatment**

Fenbendazole (when used for 5 days instead of 3; see Table 30-7), thiabendazole, and ivermectin are effective anthelmintics. This disease is a human health hazard because larvae penetrate unbroken skin. Immunosuppressed people are at risk for severe disease after being infected.

# **Prognosis**

The prognosis is guarded in young animals with severe diarrhea and/or pneumonia.

#### COCCIDIOSIS

#### Etiology

Isospora spp. are principally found in young cats and dogs. The pet is usually infested by ingesting infective oocysts from the environment. The coccidia invade and destroy villous epithelial cells.

# **Clinical Features**

Coccidia may be clinically insignificant (especially in an asymptomatic, older animal), or they may be responsible for mild to severe diarrhea, sometimes with blood. Rarely, a kitten or puppy may lose enough blood to require a blood transfusion.

# Diagnosis

Coccidiosis is diagnosed by finding oocysts on fecal flotation examination (see Fig. 33-4); however, repeated fecal examinations may be needed, and small numbers of oocysts do not ensure that the infestation is insignificant. These oocysts should not be confused with giardial cysts. If a necropsy is performed, multiple areas of the intestine should be sampled because the infection may be localized to one area. Occasionally, *Eimeria* oocysts will be seen in the feces of dogs that eat deer or rabbit excrement.

# Treatment

If coccidia are believed to be causing a problem, sulfadimethoxine or trimethoprim-sulfa should be administered for 10 to 20 days (see Table 30-7). The sulfa drug does not eradicate the coccidia but inhibits it so that body defense mechanisms can reestablish control. Amprolium (25 mg/kg administered orally q24h for 3 to 5 days) can be used in puppies but is not approved for use in dogs; it is potentially toxic in cats. Toltrazuril (15 mg/kg q24h for 3 days) has been found to decrease oocyst shedding, at least temporarily.

# **Prognosis**

The prognosis for recovery is usually good unless there are underlying problems that allowed the coccidia to become pathogenic in the first place.

# **CRYPTOSPORIDIA**

# Etiology

Cryptosporidium parvum may infect animals that ingest the sporulated oocysts. These oocysts originate from infested animals but may be carried in water. Thin-walled oocysts are produced, which can rupture in the intestine and produce autoinfection. The organism infests the brush border of small intestinal epithelial cells and causes diarrhea.

. Notes in the control of the contro

#### Clinical Features

Diarrhea is the most common clinical sign in dogs and cats, although many infested cats are asymptomatic. Dogs with diarrhea are usually under 6 months of age, but a similar age predilection has not been recognized for cats.

#### Diagnosis

Diagnosis requires finding the oocysts or a positive ELISA. *C. parvum* is the smallest of the coccidians and is easy to miss on fecal examination. Examination should be performed at ×1000 magnification. Use of acid-fast stains on fecal smears and fluorescent antibody techniques improves sensitivity. It is best to submit the feces to a laboratory experienced in diagnosing cryptosporidiosis. The laboratory must be warned that the feces may contain *C. parvum*, which is potentially infective for people. The ELISA is more sensitive than fecal examination.

# Treatment/Prognosis

There are no known reliable treatments. Immunocompetent people and cattle often spontaneously eliminate the infestation, but whether small animals do so is unknown. Most young dogs with diarrhea associated with cryptosporidiosis die or are cuthanized. Many cats have asymptomatic infestations, and those with diarrhea have an unknown prognosis.

#### **GIARDIASIS**

# Etiology

Giardiasis is caused by a protozoan, Giardia sp. Animals are infected when they ingest cysts shed from infected animals, often via water. Organisms are principally found in the small intestine, where they interfere with digestion through uncertain mechanisms. In people Giardia organisms may

occasionally ascend into the bile duct and cause hepatic problems.

#### **Clinical Features**

Signs vary from mild to severe diarrhea, which may be persistent, intermittent, or self-limiting. Typically the diarrhea is "cow patty"—like, without blood or mucus; however, there is substantial variation. Some animals experience weight loss; others do not. Diarrhea caused by *Giardia* can mimic large bowel diarrhea in some patients. In cats there may be an association between shedding giardial oocysts and shedding either cryptosporidial or coccidian oocysts.

# **Diagnosis**

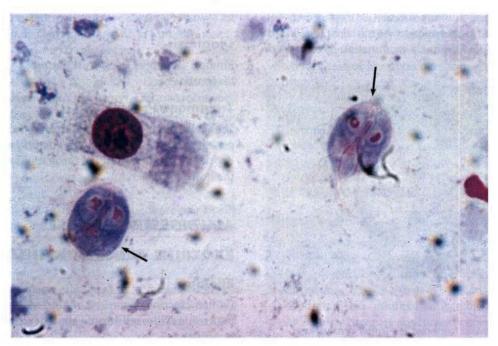
Giardiasis is diagnosed by finding motile trophozoites (Fig. 33-6) in fresh feces or duodenal washes, by finding cysts with fecal flotation techniques, or by finding giardial proteins in feces using an ELISA. Zinc sulfate solutions seem to be the best medium for demonstrating cysts (especially when centrifugal flotation is performed) because other solutions may distort them. At least three fecal examinations should be performed over the course of 7 to 10 days before discounting giardiasis. Some fecal ELISA techniques (e.g., SNAP Giardia Test, Idexx Laboratories) appear to have excellent sensitivity and are easier than centrifugal fecal flotation examinations. Washes of the duodenal lumen (performed endoscopically or surgically by instilling and then retrieving 5 to 10 ml of physiologic saline solution from the duodenal lumen) or cytologic evaluation of the duodenal mucosa

occasionally reveal *Giardia* organisms when other techniques do not.

#### **Treatment**

Because of the occasional difficulty in finding Giardia organisms (especially in animals that have had various symptomatic antidiarrheal medications), response to treatment is often the retrospective basis of diagnosis (see Table 30-7). This approach has limitations. Quinacrine is effective but no longer available. Metronidazole has few adverse effects and seems reasonably effective (approximately 85% cured after 7 days of therapy). However, clinical response to metronidazole therapy may occur in animals without giardiasis. Furazolidone (5 days of therapy) is probably as effective as metronidazole and is available as a suspension, making it easier to treat infected kittens. Albendazole (3 days of therapy in dogs, 5 days of therapy in cats) and fenbendazole (5 days of therapy in dogs or cats) are also effective, and recent data suggest that ronidazole may also be effective (see the section on tritrichomoniasis). However, none of these drugs is 100% effective, meaning that failure to respond to drug therapy does not rule out giardiasis.

There are several reasons why it can be difficult to eliminate *Giardia* spp. First, *Giardia* organisms seemingly may become resistant to some drugs. Second, immunodeficiency or concurrent host disease may make it difficult to eliminate the organism. Third, reinfection is easy because giardial cysts are rather resistant to environmental influences and relatively few are needed to reinfect a dog or person. Bathing the



**FIG 33-6**Giardia trophozoites (arrows) in a canine fecal smear that has been stained to enhance internal structures. (Magnification ×1000.) (Courtesy Dr. Tom Craig, Texas A & M University.)

patient and cleansing the environment can be very important to successful treatment in many patients. Quaternary ammonium compounds and pine tars are effective disinfectants for the premises. Fourth, sometimes other protozoal agents (e.g, *Tritrichomonas*) are mistaken for *Giardia*. Vaccination is not generally successful as a treatment modality for patients that do not respond to the aforementioned drugs.

# **Prognosis**

The prognosis for recovery is usually good, although in some cases the organisms are difficult to eradicate. Whether people may occasionally be infected with *Giardia* organisms shed from dogs is unknown.

# **TRICHOMONIASIS**

# **Etiology**

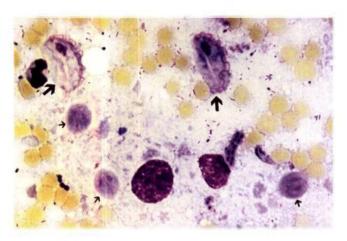
Trichomoniasis in cats appears to be caused by *Tritrichomonas foetus/suis*. Animals are probably infected by the fecaloral route.

#### **Clinical Features**

Trichomoniasis typically is associated with large bowel diarrhea, which rarely contains blood or mucus. Exotic cat breeds (e.g., Somalis, Ocicats, Bengals) are the breeds primarily affected with clinical signs. Affected cats are typically otherwise normal, although there may be anal irritation and defecation in inappropriate places. The diarrhea typically resolves spontaneously, although it may persist for months.

# Diagnosis

Diagnosis requires identifying the motile trophozoite, but live *Tritrichomonas* trophozoites can be mistaken for *Giardia* trophozoites (Fig. 33-7). Timely examination of fresh feces



#### FIG 33-7

Comparison of *Giardia* trophozoites (small arrows) and *Tritrichomonas* trophozoites (large arrows) in a smear that has been stained to enhance internal structures. Note that the *Tritrichomonas* trophozoites are larger and have one large undulating membrane. (Magnification ×1000.) (Courtesy Dr. Tom Craig, Texas A & M University.)

diluted with warm saline solution is the easiest technique, but it is insensitive. Fecal culture using the pouch technique developed for bovine venereal trichomoniasis is more sensitive.

# **Treatment/Prognosis**

Ronidazole (30 to 50 mg/kg q12h for 14 days) is the only drug currently known to safely eliminate *Tritrichomonas*, but neurologic signs have been reported with its use. If trichomoniasis is diagnosed, it is still important to look for other causes of diarrhea (e.g., *C. perfringens*, diet, *Cryptosporidium* spp.) because treatment for one of these other causes may cause resolution of the diarrhea. Most affected cats will eventually resolve the clinical signs of trichomoniasis, although diarrhea may recur if the patient undergoes stressful events (e.g., elective surgery).

#### **HETEROBILHARZIA**

# **Etiology**

Heterobilharzia americana infects dogs and establishes itself in the liver. Ova laid in the veins end up in the intestinal wall, where they elicit a granulomatous inflammation. The organism is primarily found in Gulf coast states and the southern Atlantic coast states.

#### Clinical Features

Large bowel disease is the primary sign, although the ova can be found in large and small bowel. Diarrhea, hematochezia, and weight loss are typical findings. Protein-losing enteropathy may occur, and the granulomatous reaction is associated with hypercalcemia in some dogs. Hepatic disease may be mild or severe.

#### **Diagnosis**

Finding the ova in feces or in mucosal biopsy specimens is diagnostic.

# **Treatment/Prognosis**

Fenbendazole plus praziquantel is successful in killing the parasite and the ova. However, the prognosis is seemingly dependent on the severity of the granulomatous reaction in the bowel and liver.

# MALDIGESTIVE DISEASE

# **EXOCRINE PANCREATIC INSUFFICIENCY**

#### Etiology

Canine exocrine pancreatic insufficiency (EPI) is caused by pancreatic acinar cell atrophy or destruction associated with pancreatitis.

#### **Clinical Features**

EPI is principally found in dogs and rarely in cats. Chronic small intestinal diarrhea, a ravenous appetite, and weight

loss are classic findings. Steatorrhea (i.e., slate-gray stools) is sometimes seen, and animals occasionally have weight loss without diarrhea. The diarrhea is classified as a small bowel problem (because of the weight loss and the nature of the diarrhea). Physical examination and routine clinical pathologic findings are not diagnostic. The most sensitive and specific test for canine EPI is measurement of serum trypsin-like immunoreactivity (TLI; i.e., low activity in affected dogs). Finding undetectable levels of canine pancreatic lipase immunoreactivity (cPLI) might be suggestive of EPI but is not as specific as decreased TLI. Treatment involves the administration of pancreatic enzymes with the food and manipulation of dietary fat content. The reader is referred to Chapter 40 for more information on EPI.

#### MALABSORPTIVE DISEASES

# **ANTIBIOTIC-RESPONSIVE ENTEROPATHY**

# Etiology

Antibiotic-responsive enteropathy (ARE) is a syndrome in which the duodenum or jejunum (or both) has high numbers of bacteria (i.e., usually >105 colony forming units/ml) and the host seemingly has an abnormal response to these bacteria. The abnormal host response is important, as seen by the fact that dogs with comparable numbers of bacteria in their small intestine (i.e., ≥108/ml of fasting fluid) do not have clinical disease. The bacteria may be present because of (1) an anatomic defect allowing retention of food (e.g., a partial stricture or an area of hypomotility), (2) other diseases (e.g., intestinal mucosal disease), (3) impaired host defenses (i.e., hypochlorhydria, IgA deficiency), or (4) no identifiable reason. Bacteria causing ARE are usually present in mixed culture, and they probably gain access to the alimentary tract by being swallowed (i.e., originating from the oral cavity or in the food). Any species of bacteria may be present, but Escherichia coli, enterococci, and anaerobes such as Clostridium spp. seem to be especially common. Presumably, enterocytes are damaged by deconjugation of bile acids, fatty acid hydroxylation, generation of alcohols, and potentially other mechanisms.

#### Clinical Features

ARE can be found in any dog. Clinical signs are principally diarrhea or weight loss (or both), although vomiting may also occur.

# **Diagnosis**

Currently available diagnostic tests for ARE have questionable sensitivity and specificity. Quantitative duodenal fluid cultures are difficult to obtain in most private practices and are difficult to interpret. The major value of small bowel cultures may be in patients in which the diagnosis of ARE is not in doubt but the patient is no longer responding to commonly used antibiotics, and the question is which antibiotic(s) might be effective. Serum cobalamin and folate concentra-

tions have questionable sensitivity and specificity for this disorder. Duodenal mucosal cytology and histopathology are routinely nondiagnostic for ARE. Because of these problems in diagnosing ARE, many clinicians treat and observe for response.

#### **Treatment**

Because of the difficulty in diagnosing ARE, therapy is reasonable when this disorder is suspected. Therapy consists of antibiotics and the removal of potential causes (e.g., blind or stagnant loops of intestine). Because mixed bacterial populations are expected, broad-spectrum antibiotics effective against aerobic and anaerobic bacteria are recommended. Tylosin (10 to 40 mg/kg q12h) is often effective. A combination of metronidazole (15 mg/kg q24h) and enrofloxacin (7 mg/kg q24h) also seems effective in many patients. Recent work suggests that simultaneously feeding a high-quality, highly digestible or hypoallergenic diet makes the antibiotic therapy more effective.

Occasionally, a pure culture of a specific bacteria will be found in the duodenum, such that a specific antibiotic is required. However, such cases appear to be rare. When treating dogs with suspected ARE, the clinician should wait 2 to 3 weeks before deciding that the therapy was not effective. Because there may be an underlying cause that cannot be corrected, some animals need long-term to indefinite antibiotic therapy. This may be especially true in dogs that have had repeated episodes of illness since they were a few months old. It seems as though these patients may have some genetic predisposition to ARE, probably because of a defect in host defense mechanisms. The clinician should warn the owner that the goal is typically control, not cure. Patients that have nearly constant diarrhea when not being treated may need antibiotics and dietary therapy indefinitely. Patients who have episodes every 2 to 4 months might best be treated when they relapse as opposed to having them on antibiotics constantly

# **Prognosis**

The prognosis is usually good for control of ARE, but the clinician must be concerned with possible underlying causes.

#### **DIETARY-RESPONSIVE DISEASE**

# **Etiology**

Dietary-responsive disease is an all-inclusive term that includes dietary allergy (a hyperimmune response to a dietary antigen) and dietary intolerance (a nonimmune-mediated response to a dietary substance). From a clinical standpoint, there is minimal value in distinguishing between the two unless there are concurrent cutaneous signs of allergic disease.

#### Clinical Features

Affected patients may have vomiting and/or diarrhea (large and/or small bowel) as well as allergic skin disease.

# Diagnosis

Diagnosis consists of showing response to feeding an elimination diet that is appropriate for the patient (see the discussion of dietary management in Chapter 30). There is typically minimal value in distinguishing between allergy and intolerance. Tests for IgE antibodies in the patient's blood to specific antigens are not as valuable as seeing the response to an elimination diet. The diet must be carefully chosen; it must consist of nonallergenic substances or foods to which the patient has not previously been exposed. Most animals respond to an appropriate diet within 3 weeks, although some take longer.

#### **Treatment**

Most patients that respond can simply be fed the diet to which they responded in the dietary trial (assuming that it is balanced). Rare patients develop allergies to the elimination diet and require different elimination diets to be fed on rotating 2- to 3-week cycles.

# **Prognosis**

The prognosis is usually good.

# SMALL INTESTINAL INFLAMMATORY BOWEL DISEASE

#### Clinical Features

IBD involves *idiopathic* intestinal inflammation. IBD can affect any portion of the canine or feline intestine. Although the cause of IBD is unknown, it is speculated to involve an exaggerated or inappropriate response by the immune system to bacterial and/or dietary antigens as at least part of the mechanism. The clinical and histologic features of IBD can closely resemble those of alimentary lymphoma (see p. 467). Lymphocytic-plasmacytic enteritis (LPE) is the most commonly diagnosed form of canine and feline IBD. Chronic small intestinal diarrhea is common, but some patients have weight loss with normal stools. If the duodenum is severely affected, vomiting may be the major sign, and diarrhea can be either mild or absent. Protein-losing enteropathy can occur with the more severe forms.

Eosinophilic gastroenterocolitis (EGE) is usually an allergic reaction to dietary substances (e.g., beef, milk) and as such is not IBD. However, the clinical signs do not always respond to dietary change and may represent true IBD in some dogs. It is less common than LPE. Some cats have eosinophilic enteritis as part of a hypereosinophilic syndrome (HES). The cause of feline HES is unknown, but immune-mediated and neoplastic mechanisms may be responsible. Less severely affected cats without HES seem to have a condition similar to canine EGE.

#### Diagnosis

Because IBD is *idiopathic* intestinal inflammation, it is a diagnosis of exclusion; it is not just a histologic diagnosis. No physical examination, historic, clinical pathology, imaging, or histologic findings are diagnostic of IBD. Diag-

nosis requires elimination of known causes of diarrhea plus histology showing mucosal inflammatory infiltrates, architectural changes (e.g., villus atrophy, crypt changes), and/or epithelial changes. Mucosal cytologic evaluation is unreliable for diagnosing lymphocytic inflammation because lymphocytes and plasma cells are normally present in intestinal mucosa. Histologic diagnosis of mucosal inflammation is unfortunately subjective, and biopsy samples are frequently overinterpreted. "Mild" LPE often refers to essentially normal tissue. Even descriptions of "moderate" or "severe" LPE may be dubious because of substantial inconsistency among pathologists. It can be extremely difficult to distinguish a well-differentiated lymphocytic lymphoma from severe LPE, even with full-thickness samples. Some animals with intense dietary reactions have biopsy findings that resemble lymphoma. If the biopsy specimens are of marginal quality (either from the standpoint of size or artifacts present), it is easy to mistakenly diagnose LPE instead of lymphoma if the latter is causing a secondary tissue reaction. Recent data document that biopsy of more than one site (e.g., duodenum and ileum, as opposed to just duodenum) is sometimes critical in finding inflammatory (and neoplastic) changes. Diagnosis of feline LPE is similar to that of canine LPE, but it is important to note that cats with IBD may have mild to moderate mesenteric lymphadenopathy, and such lymphadenopathy is not diagnostic of intestinal lymphoma.

Diagnosis of EGE is similar to diagnosis of LPE. Dogs with EGE may have eosinophilia and/or concurrent eosinophilic respiratory or cutaneous dietary allergies with pruritus. German Shepherd dogs seem to be overrepresented. Diagnosis of feline EGE centers on finding intestinal eosinophilic infiltrates; however, splenic, hepatic, lymph node, and bone marrow infiltrates and peripheral eosinophilia are common.

#### **Treatment**

Canine LPE treatment begins with elimination diets and antibiotics in case what appears to be IBD is actually dietary intolerance or ARE. Other therapy depends on the severity of the LPE. Somewhat more severe disease warrants metronidazole with or without high-dose corticosteroid therapy (e.g., prednisolone, 2.2 mg/kg/day or budesonide in steroid-intolerant patients). More severe disease, especially if associated with hypoalbuminemia, usually requires immunosuppressives (e.g., azathioprine or cyclosporine). Cyclosporine seems to be reasonably effective and works faster than azathioprine administered every other day; however, it is also more expensive. Elemental diets, although expensive, can be invaluable in severely emaciated or severely hypoproteinemic patients with severe inflammation as a way to feed the patient and the intestinal mucosa without causing more mucosal irritation. Failure of a dog to respond to "appropriate" therapy can be the result of inadequate therapy, owner noncompliance, or misdiagnosis (i.e., diagnosing LPE when the problem is lymphoma).

Feline LPE treatment is somewhat similar to that for canine LPE. Highly digestible elimination diets may be cura-

tive if what was thought to be IBD is actually food intolerance, and therapeutic diets should always be used if the cat will eat them. High doses of corticosteroids are typically administered early in cats because of their beneficial effects and the cat's relative resistance to iatrogenic hyperadrenocorticism. Prednisolone is preferred to prednisone in the cat, and methylprednisolone is typically more effective than prednisolone. Budesonide is primarily indicated in cats that cannot tolerate the systemic effects of steroids (e.g., those with diabetes mellitus). Low-dose metronidazole (10 to 15 mg/kg administered orally q12h), either alone or in combination with corticosteroids and diet, may also be effective. Azathioprine is not used in cats; instead, chlorambucil is used for cats with biopsy-proven, severe LPE that does not respond to other therapy (see Chapter 79) or for cats with well-differentiated lymphoma. Enteral or parenteral nutritional supplementation may be useful in emaciated cats (see Chapter 30). Parenteral administration of cobalamin to cats with severely decreased serum concentrations may aid or be necessary for remission of diarrhea. If the cat responds to this therapy, the elimination diet should be continued while the medications are gradually tapered one at a time.

Canine EGE treatment should focus on a strict hypoallergenic diet (e.g., fish and potato, turkey and potato). Partially hydrolyzed diets may also be helpful, but they are not a panacea for all GI dietary allergies/intolerances. It is important to determine what the dog was fed previously when selecting the dietary therapy. If signs do not resolve with dietary therapy, the addition of corticosteroid therapy is usually curative. Animals usually respond better to elimination diets than to corticosteroids. Sometimes, an animal initially responds to dietary management but relapses while still eating this diet because it becomes allergic to one of the ingredients. This situation necessitates administration of another elimination diet. In some animals that are very prone to developing such intolerances, switching back and forth from one elimination diet to another at 2-week intervals helps to prevent this relapse from happening. (See Chapter 30 for more information on these therapies.)

Feline EGE associated with hypereosinophilic syndrome usually requires high-dose corticosteroid therapy (i.e., prednisolone, 4.4 to 6.6 mg/kg/day); response is often poor. Cats with eosinophilic enteritis not caused by HES often respond favorably to elimination diets plus corticosteroid therapy.

If the dog or cat responds clinically, then the therapy should be continued without change for another 2 to 4 weeks to ensure that the clinical improvement is the result of the therapy and not an unrelated transient improvement. Once the clinician is convinced that the prescribed therapy is responsible for the improvement seen, the animal should be slowly weaned from the drugs, starting with those that have the greatest potential for adverse effects. If antiinflammatory or immunosuppressive therapy was initially required, the clinician should attempt to maintain the pet on every-other-day corticosteroid and azathioprine therapy. If that regimen is successful, then the lowest effective dose of each should be slowly determined. Only one change should be made at a

time, and the dose should not be decreased more frequently than once every 2 to 3 weeks, if possible. If a homemade diet was used initially, the clinician should seek to transition the patient to a complete, balanced commercial elimination diet. Dietary and antibiotic therapy are usually the last to be altered. There is no obvious benefit to rebiopsying patients that are clinically improving.

# **Prognosis**

The prognosis for dogs and cats with LPE is often good, if therapy is begun before the patient is emaciated. Severe hypoalbuminemia and a very poor body condition are thought to be suggestive that the patient may have more difficulty responding. A markedly low serum cobalamin concentration in the dog might be a poor prognostic sign, but that is uncertain. Many animals will need to be on a special diet for the rest of their lives. Many with moderate to severe disease will need prolonged medical therapy, which should be tapered cautiously. Iatrogenic Cushing's syndrome should be avoided. Severely affected animals may initially benefit from enteral or parenteral nutritional therapy. Although the relationship is unclear, LPE has been suggested to be a potentially prelymphomatous lesion (see p. 460 for immunoproliferative enteropathy in Basenjis); however, this is uncertain. If a dog or cat with a prior diagnosis of LPE is later diagnosed as having lymphoma, it may be just as likely that either the initial diagnosis of IBD was wrong (i.e., the patient had lymphoma) or that the lymphoma developed independently of the IBD.

# LARGE INTESTINAL INFLAMMATORY BOWEL DISEASE

# Clinical Features

In the author's practice, Clostridium colitis, parasites, dietary intolerance, and fiber-responsive diarrhea are responsible for most cases referred and previously diagnosed as having "intractable" large bowel "IBD." Canine lymphocytic-plasmacytic colitis (LPC) typically causes large bowel diarrhea (i.e., soft stools with or without blood or mucus; no appreciable weight loss). In general, affected dogs are fundamentally healthy except for soft stools. In cats hematochezia is the most common clinical sign, and diarrhea is the second most common sign. Feline LPC may occur by itself or concurrently with LPE, whereas canine large bowel IBD seems to be infrequently associated with small bowel IBD.

# Diagnosis

Diagnosis (i.e., excluding other causes and finding mucosal histologic changes) is similar to that for small bowel IBD. In particular, *Tritrichomonas* can cause substantial mononuclear infiltrates into feline colonic mucosa.

# Treatment

Steroids, metronidazole, sulfasalazine (Azulfidine), mesalamine, or olsalazine may be used in dogs with moderate to severe LPC. Corticosteroids and/or metronidazole may be

effective by themselves and/or allow lower doses of sulfasalazine to be successful. Hypoallergenic and fiber-enriched diets are often very helpful. It is critical to eliminate colonic fungal infections before begining immunosuppressive therapy.

High-fiber and hypoallergenic diets are also often beneficial in cats; in fact, most "intractable" feline LPC cases seen in the author's practice are ultimately determined to be related to diet. Most cats with LPC respond well to prednisolone and/or metronidazole, and sulfasalazine is rarely needed.

# **Prognosis**

The prognosis for patients with colonic IBD tends to be better than for small bowel IBD.

# GRANULOMATOUS ENTERITIS/ GASTRITIS

Canine granulomatous enteritis/gastritis is uncommon, and it can be diagnosed only histopathologically. The clinician should search diligently for an etiology (e.g., fungal). Clinical signs are similar to those of other forms of IBD. Although compared to Crohn's disease in people, the two are dissimilar. If the disease is localized, surgical resection should be considered if the clinician is sure that there is not a systemic cause (e.g., fungal). If it is diffuse, corticosteroids, metronidazole, antibiotics, azathioprine, and dietary therapy should be considered. Too few cases have been described and treated to allow generalizations. The prognosis is poor.

Feline granulomatous enteritis is a rare type of IBD that causes weight loss, protein-losing enteropathy, and perhaps diarrhea; it also requires histopathologic confirmation. Affected cats seem to respond to high-dose corticosteroid therapy, but attempts to reduce the dose of glucocorticoids may cause recurrence of clinical signs. The prognosis is guarded.

# IMMUNOPROLIFERATIVE ENTEROPATHY IN BASENJIS

#### Etiology

Immunoproliferative enteropathy in Basenjis is an intense lymphocytic-plasmacytic small intestinal infiltrate often associated with villous clubbing, mild lacteal dilation, gastric rugal hypertrophy, lymphocytic gastritis, and/or gastric mucosal atrophy. It probably has a genetic basis or predisposition, and intestinal bacteria may play an important role.

#### **Clinical Features**

The disease tends to be a severe form of LPE that waxes and wanes, particularly as the animal is stressed (e.g., traveling, disease). Weight loss, small intestinal diarrhea, vomiting, and/or anorexia are commonly seen. Most affected Basenjis start showing clinical signs by 3 to 4 years of age.

#### Diagnosis

Marked hypoalbuminemia and hyperglobulinemia are common, especially in advanced cases. The early stages of the disease resemble many other intestinal disorders. In advanced cases the clinical signs are so suggestive that a presumptive diagnosis is often made without biopsy.

However, because other diseases (e.g., lymphoma, histoplasmosis) may mimic immunoproliferative enteropathy, alimentary tract biopsy is needed before aggressive immunosuppressive therapy is begun.

#### **Treatment**

Therapy may include highly digestible, elimination, or elemental diets; antibiotics for ARE (see p. 457); high-dose corticosteroids; metronidazole; and azathioprine. Response to therapy is variable, and affected dogs that respond are at risk for relapse, especially if stressed.

Although a genetic basis is suspected, not enough is known to be able to confidently recommend a breeding program. Performing biopsy of the intestines of asymptomatic dogs to identify animals in which the disease will develop is dubious because clinically normal Basenjis may have lesions similar to those of dogs with diarrhea and weight loss, although the changes tend to be milder.

# **Prognosis**

Many affected animals die 2 to 3 years after diagnosis. The prognosis is poor for recovery, but some dogs can be maintained for prolonged periods of time with careful monitoring and care. In a few dogs lymphoma later develops.

#### ENTEROPATHY IN CHINESE SHAR-PEIS

#### Etiology

Chinese Shar-Peis have a poorly characterized enteropathy that may be unique to them or may be a severe form of IBD. Chinese Shar-Peis have immune system abnormalities that may predispose them to exaggerated inflammatory reactions.

#### Clinical Features

Diarrhea and/or weight loss (i.e., small intestinal dysfunction) are the main clinical signs.

## Diagnosis

Small intestinal biopsy is necessary for diagnosis. Eosinophilic and lymphocytic-plasmacytic intestinal infiltrates are typically found. Serum cobalamin concentrations are often quite low.

# **Treatment**

The animal is treated for IBD (i.e., elimination diets and immunosuppressive drugs) and ARE.

# **Prognosis**

Affected Chinese Shar-Peis have a guarded prognosis.

# PROTEIN-LOSING ENTEROPATHY

# CAUSES OF PROTEIN-LOSING ENTEROPATHY

Any intestinal disease that produces sufficient inflammation, infiltration, congestion, or bleeding can produce a protein-

losing enteropathy (PLE; or gastropathy if it affects the stomach; see Box 28-10). IBD and alimentary tract lymphoma have been suggested as particularly common causes in adult dogs, whereas hookworms and chronic intussusception are common causes in very young dogs. When IBD is responsible, it is usually a severe form of LPE, although EGE or granulomatous disease may be responsible. Immunoproliferative enteritis of Basenjis, GI ulceration/erosion, and bleeding tumors may also produce PLE. Lymphangiectasia appears to be more common (in dogs) than was once thought; the problem is that it can be difficult to diagnose. Cats infrequently have PLE, but when it occurs, it is usually caused by LPE or lymphoma. Therapy should be directed at managing the underlying cause.

#### INTESTINAL LYMPHANGIECTASIA

# **Etiology**

Intestinal lymphangiectasia (IL) is a disorder of the intestinal lymphatic system of dogs. Lymphatic obstruction causes dilation and rupture of intestinal lacteals with subsequent leakage of lymphatic contents (i.e., protein, lymphocytes, and chylomicrons) into the intestinal submucosa, lamina propria, and lumen. Although these proteins may be digested and resorbed, excessive loss exceeds the intestine's ability to resorb them, thus resulting in hypoalbuminemia. Leakage of lymphatic fat into the intestinal wall may cause granuloma formation, which exacerbates lymphatic obstruction. Not reported in cats, the condition has many potential causes in dogs (e.g., lymphatic obstruction, pericarditis, infiltrative mesenteric lymph node disease, infiltrative intestinal mucosal disease, congenital malformations). Most cases of symptomatic IL are idiopathic.

# **Clinical Features**

Yorkshire Terriers, Soft Coated Wheaten Terriers, and Lundehunds appear to be at higher risk than other breeds. Soft Coated Wheaten Terriers also have an unusually high incidence of protein-losing nephropathy. The first sign of disease caused by IL may be transudative ascites. Diarrhea is inconsistent and may occur early or late in the course of the disease, if at all. Intestinal lipogranulomas (i.e., white nodules in the intestinal serosa or mesentery) are sometimes found at surgery. They are probably secondary to IL (i.e., fat leaking out of dilated lymphatic vessels), but they might worsen existing IL by further obstructing lymphatics.

# Diagnosis

Clinical pathologic evaluation is not diagnostic, but hypoalbuminemia and hypocholesterolemia are expected. Although panhypoproteinemia is classically attributed to PLE, animals that were initially hyperglobulinemic may lose most of their serum proteins and still have normal serum globulin concentrations. Lymphopenia is common but inconsistent. Diagnosis requires intestinal histopathology. Feeding the animal fat the night before the biopsy seems to make lesions more obvious, and classic mucosal lesions may be seen endoscopically (Fig. 33-8). Endoscopic biopsies are often diagnos-



FIG 33-8
Endoscopic image of the duodenum of a dog with lymphangiectasia. The large white "dots" are dilated lacteals in the tips of the villi.

tic if done appropriately, but surgical biopsies are sometimes required. If full-thickness surgical biopsies are performed, serosal patch grafting and nonabsorbable suture material may decrease the risk of dehiscence. IL may be localized to one area of the intestines (e.g., ileum).

#### **Treatment**

The underlying cause of IL is rarely determined, necessitating reliance on symptomatic therapy. An ultra–low-fat diet essentially devoid of long-chain fatty acids helps to prevent further intestinal lacteal engorgement and subsequent protein loss. Prednisolone (1.1 to 2.2 mg/kg/day) or azathioprine (2.2 mg/kg q48h) or cyclosporine (3-5 mg/kg q24h to q12h) sometimes lessens inflammation around the lipogranulomas and improves lymphatic flow.

Monitoring serum albumin concentration may be the best way of assessing response to therapy. If the animal improves with dietary therapy, it should probably be fed that diet indefinitely. Azathioprine or cyclosporine therapy might help solidify response to dietary therapy and maintain remission.

# **Prognosis**

The prognosis is variable, but most dogs respond well to ultra-low-fat diets, although some require prednisolone in addition to the diet. A few dogs die despite dietary and prednisolone therapy.

# PROTEIN-LOSING ENTEROPATHY IN SOFT-COATED WHEATEN TERRIERS

# Etiology

Soft Coated Wheaten Terriers (SCWTs) have a predisposition to PLE and protein-losing nephropathy. The cause is

uncertain, although food hypersensitivity has been reported to be present in some affected dogs.

# **Clinical Features**

Individual dogs may have PLE or protein-losing nephropathy (or both). Typical clinical signs may include vomiting, diarrhea, weight loss, and ascites. Affected dogs are often middle aged when diagnosed.

# Diagnosis

Panhypoproteinemia and hypocholesterolemia are common, as with any PLE. Histopathology of intestinal mucosa may reveal lymphangiectasia, lymphangitis, or supposedly IBD.

# **Treatment/Prognosis**

Treatment is typically as for lymphangiectasia and/or IBD. The prognosis appears guarded to poor for clinically ill animals, with most dying within a year of diagnosis.

# **FUNCTIONAL INTESTINAL DISEASE**

#### IRRITABLE BOWEL SYNDROME

# Etiology

Irritable bowel syndrome (IBS) in people is characterized by diarrhea, constipation, and/or cramping (usually of the large intestines) in which an organic lesion cannot be identified. It is an idiopathic large bowel disease in which all known causes of diarrhea have been eliminated and a "functional" disorder is presumed. IBS in dogs is different and primarily involves an idiopathic, chronic large bowel diarrhea in which parasitic, dietary, bacterial, and inflammatory causes have been eliminated. There are probably various causes of this syndrome in dogs.

#### **Clinical Features**

Chronic large bowel diarrhea is the principal sign. Fecal mucus is common, blood in the feces is infrequent, and weight loss is very rare. Some dogs with IBS are small breeds that are heavily imprinted on a single family member. Clinical signs may develop following separation of the dog from the favored person. Other dogs with IBS are nervous and high-strung (e.g., police or guard dogs, especially German Shepherd Dogs). Some dogs have no apparent initiating cause.

# Diagnosis

Diagnosis consists of eliminating known causes by physical examination, clinical pathologic data, fecal analysis, colonoscopy/biopsy, and appropriately performed therapeutic trials.

## **Treatment**

Treatment with fiber-supplemented diets (i.e., ≥7% to 9% fiber on a dry matter basis) is often helpful (see p. 398). Many animals must receive fiber chronically to prevent relapse.

Anticholinergics occasionally are useful (e.g., propantheline, 0.25 mg/kg; or dicyclomine, 0.15 mg/kg up to q8h, as needed).

# **Prognosis**

The prognosis is good; in most animals the signs are controlled by diet or medical management.

# INTESTINAL OBSTRUCTION

# SIMPLE INTESTINAL OBSTRUCTION

# Etiology

Simple intestinal obstruction (i.e., the intestinal lumen is obstructed but without peritoneal leakage, severe venous occlusion, or bowel devitalization) is usually caused by foreign objects. Infiltrative disease and intussusception may also be responsible.

# **Clinical Features**

Simple intestinal obstructions usually cause vomiting with or without anorexia, depression, or diarrhea. Abdominal pain is uncommon. The more orad the obstruction is, the more frequent and severe the vomiting tends to be. If the intestine becomes devitalized and septic peritonitis results, the obstruction becomes complicated and the animal may be presented in a moribund state or in septic shock (systemic inflammatory response syndrome, or SIRS).

# **Diagnosis**

Abdominal palpation, plain abdominal radiographs, or ultrasonographic imaging can be diagnostic if they reveal a foreign object, mass, or obvious obstructive ileus (see Fig. 29-5, A). Masses or dilated intestinal loops may be found with either technique. Abdominal ultrasonography tends to be the most sensitive technique (unless the intestines are filled with gas) and can reveal dilated or thickened intestinal loops that are not obvious on radiographs (e.g., poor serosal contrast caused by abdominal fluid or lack of abdominal fat) or palpation. If it is difficult to distinguish obstruction from physiologic ileus, abdominal contrast radiographs may be considered. Many intestinal foreign bodies cause hypochloremic, hypokalemic metabolic alkalosis, a metabolic change that is supposedly suggestive of gastric outflow obstruction.

Finding a foreign object is usually sufficient to establish a diagnosis. If an abdominal mass or an obvious obstructive ileus is found, a presumptive diagnosis of obstruction is made, and ultrasonography or exploratory surgery should be planned. Aspirate cytologic evaluation of masses may be used to diagnose some diseases (e.g., lymphoma) before surgery.

#### **Treatment**

Once intestinal obstruction is diagnosed, the clinician should perform routine preanesthetic laboratory tests (serum electrolyte and acid-base abnormalities are common in vomiting animals), stabilize the animal, and promptly proceed to surgery. Vomiting of gastric origin classically produces a hypokalemic, hypochloremic metabolic alkalosis and paradoxical aciduria, whereas vomiting caused by intestinal obstruction may produce metabolic acidosis and varying degrees of hypokalemia. However, these changes cannot be predicted even when the cause of the vomiting is known, making serum electrolyte and acid-base determinations important in therapy planning.

# **Prognosis**

If septic peritonitis is absent and massive intestinal resection is not necessary, the prognosis is usually good.

# INCARCERATED INTESTINAL OBSTRUCTION

# **Etiology**

Incarcerated intestinal obstruction involves a loop of intestine trapped or "strangulated" as it passes through a hernia (e.g., abdominal wall, mesenteric) or similar rent. The entrapped intestinal loop quickly dilates, accumulating fluid in which bacteria flourish and release endotoxins. SIRS occurs rapidly. This is a true surgical emergency, and animals deteriorate quickly if the entrapped loop is not removed.

## **Clinical Features**

Dogs and cats with incarcerated intestinal obstruction typically have acute vomiting, abdominal pain, and progressive depression. Palpation of the entrapped loop often causes severe pain and occasionally vomiting. On physical examination, "muddy" mucous membranes and tachycardia may be noted, suggesting endotoxic shock.

#### Diagnosis

A presumptive diagnosis is made by finding a distended, painful intestinal loop, especially if the loop is contained within a hernia. Radiographically, a markedly dilated segment of intestine is detected (Fig. 33-9) that is sometimes obviously outside the peritoneal cavity. Otherwise, an obviously strangulated loop of intestine will be found at exploratory surgery.

# Treatment

Immediate surgery and aggressive therapy for endotoxic shock are indicated. Devitalized bowel should be resected, with care taken to avoid spillage of septic contents into the abdomen.

# **Prognosis**

The prognosis is guarded. Rapid recognition and prompt surgery are necessary to prevent mortality.

# MESENTERIC TORSION/VOLVULUS

# Etiology

In mesenteric torsion/volvulus, the intestines twist about the root of the mesentery, causing severe vascular compromise.

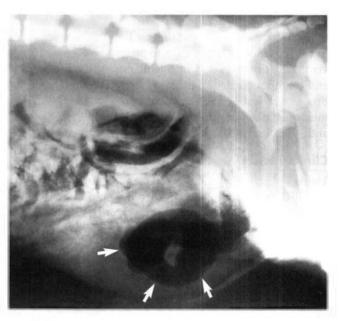


FIG 33-9

Lateral abdominal radiograph of a dog with a ruptured prepubic tendon and incarcerated intestinal obstruction. Note the dilated section of intestine in the area of the hernia (arrows). (From Allen D, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)

Much of the intestine is typically devitalized by the time surgery is performed.

# **Clinical Features**

This uncommon cause of intestinal obstruction principally occurs in large dogs (especially German Shepherd Dogs). Mesenteric torsion is denoted by an acute onset of severe nausea, retching, vomiting, abdominal pain, and depression. Bloody diarrhea may or may not occur. Abdominal distention is not as evident as it is in animals with gastric dilation/volvulus (GDV).

# Diagnosis

Abdominal radiographs are often diagnostic and typically show widespread, uniform ileus (see Fig. 29-6).

#### **Treatment**

Immediate surgery is necessary. The intestines must be properly repositioned, and devitalized bowel must be resected.

# **Prognosis**

The prognosis is extremely poor; most animals die despite heroic efforts. Animals that live may develop short bowel syndrome if massive intestinal resection is necessary.

#### LINEAR FOREIGN OBJECTS

#### Etiology

Numerous objects can assume a linear configuration in the alimentary tract (e.g., string, thread, nylon stockings, cloth).

The foreign object lodges or fixes at one point (e.g., the base of the tongue, pylorus), and the rest trails off into the intestines. The small intestine seeks to propel the object aborally via peristaltic waves and in this manner gathers around it and becomes pleated. As the intestines continue trying to propel it aborally, the linear object cuts or "saws" into the intestines, often perforating them at multiple sites on the antimesenteric border. Fatal peritonitis can result.

## **Clinical Features**

Linear foreign objects appear to be more frequent in cats than in dogs. Vomiting food, bile, and/or phlegm is common, but some animals show only anorexia or depression. A few (especially dogs with chronic linear foreign bodies) can be relatively asymptomatic for days to weeks while the foreign body continues to embed itself in the intestines.

# Diagnosis

The history may be suggestive of a linear foreign body (e.g., the cat was playing with cloth or string). Bunched, painful intestines are occasionally detected by abdominal palpation. The object is sometimes seen lodged at the base of the tongue; however, failure to find a foreign object at the base of the tongue does not eliminate linear foreign body as a diagnosis. Even when such objects lodge under the tongue, they can be very difficult to find despite a careful, thorough oral examination; some become embedded in the frenulum. If necessary, chemical restraint (e.g., ketamine, 2 mg/kg administered intravenously) should be used to allow adequate oral examination.

Foreign objects lodged at the pylorus and trailing off into the duodenum must be diagnosed by abdominal palpation, imaging, or endoscopy. The objects themselves are infrequently seen radiographically and only rarely produce dilated intestinal loops suggesting anatomic ileus; the proximity to the stomach and the pleating of the intestines around the object usually prevents the intestines from dilating. Plain radiographs may reveal small gas bubbles in the intestines, especially in the region of the duodenum, and obvious intestinal pleating may occasionally be seen (Fig. 33-10). If contrast radiographs are performed, they typically reveal a pleated or bunched intestinal pattern, which is diagnostic of linear foreign body. Finally, these objects are sometimes seen endoscopically lodged at the pylorus.

## **Treatment**

Abdominal surgery is often needed to remove linear foreign objects. However, if the animal is otherwise healthy, if the linear foreign object has been present for only 1 or 2 days, and if it is fixed under the tongue, the object may be cut loose to see if it will now pass through the intestines without further problem. Surgery is indicated if the animal does not feel better 12 to 24 hours after the object is cut free from its point of fixation.

If there is doubt as to the length of time that the object has been present, or if it is fixed at the pylorus, surgery is usually a safer therapeutic approach. Endoscopic removal occasionally succeeds, but the clinician must be careful because it is easy to rupture devitalized intestine and cause peritonitis. If the clinician can pass the tip of the endoscope to near the aborad end of the object and pull it out by grabbing the aborad end, surgery is sometimes unnecessary.

# **Prognosis**

The prognosis is usually good if severe septic peritonitis is absent and massive intestinal resection is unnecessary. If a linear foreign object has been present a long time, it may embed itself in the intestinal mucosa, making intestinal resection necessary. When massive intestinal resection is necessary, short bowel syndrome can result; this condition has a guarded to poor prognosis.

#### INTUSSUSCEPTION

# **Etiology**

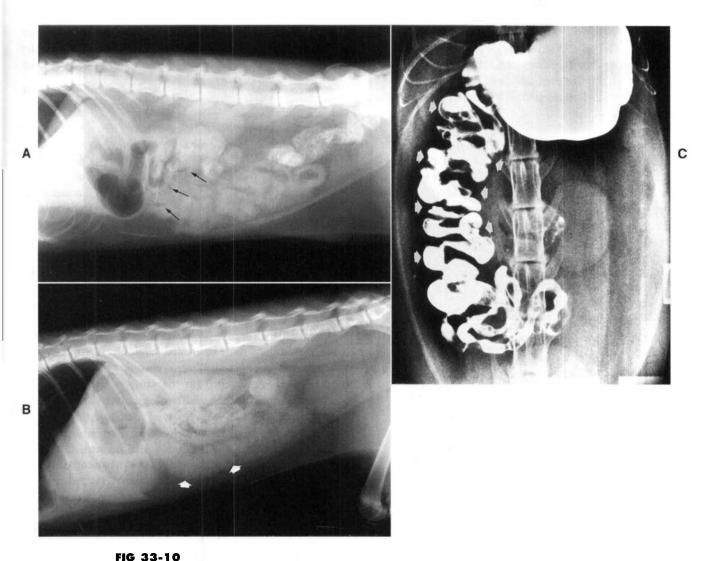
Intussusception is a telescoping of one intestinal segment (the intussusceptum) into an adjacent segment (the intussuscipiens). It may occur anywhere in the alimentary tract, but ileocolic intussusceptions (i.e., the ileum entering the colon) seem more common. Ileocolic intussusceptions seem to be associated with active enteritis (especially in young animals), which ostensibly disrupts normal motility and promotes the smaller ileum to intussuscept into the larger diameter colon. However, ileocolic intussusception may occur in animals with acute renal failure, leptospirosis, prior intestinal surgery, and other problems.

# **Clinical Features**

Acute ileocolic intussusception causes obstruction of the intestinal lumen and congestion of the intussusceptum's mucosa. Scant bloody diarrhea, vomiting, abdominal pain, and a palpable abdominal mass are common. Chronic ileocolic intussusceptions typically produce less vomiting, abdominal pain, and hematochezia. These animals often have intractable diarrhea and hypoalbuminemia because of protein loss from the congested mucosa. PLE in a young dog without hookworms or a puppy that seems to be having an unexpectedly long recovery from parvoviral enteritis should prompt suspicion of chronic intussusception. Acute jejunojejunal intussusceptions usually do not cause hematochezia. Mucosal congestion can be more severe than that in ileocolic intussusception; intestinal devitalization eventually occurs, and bacteria and their toxins gain access to the peritoneal cavity.

# **Diagnosis**

Palpation of an elongated, obviously thickened intestinal loop establishes a presumptive diagnosis; however, some infiltrative diseases produce similar findings. Ileocolic intussusceptions that are short and do not extend far into the descending colon may be especially difficult to palpate because they are high up and under the rib cage. Occasional intussusceptions "slide" in and out of the colon and can be



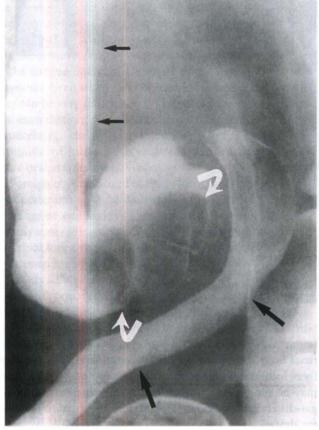
A, Plain abdominal radiograph of a cat with a linear foreign body lodged at the pylorus. Note the small gas bubbles in the mass of intestines (arrows). B, Plain abdominal radiograph of a cat with a linear foreign body. Note the obviously pleated small bowel (arrows). C, Contrast radiograph of a cat with a linear foreign body. Note the pleated, bunched pattern of intestines (arrows). (A from Allen D, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)

missed during abdominal palpation. If the intussusception protrudes as far as the rectum, it may resemble a rectal prolapse. Therefore if tissue is protruding from the rectum, the clinician should perform a careful rectal palpation to ascertain that a fornix exists (i.e., it is a rectal prolapse) as opposed to an intussusception (in which a fornix cannot be found).

Plain abdominal radiographs infrequently allow the diagnosis of ileocolic intussusceptions because they usually cause minimal intestinal gas accumulation. A properly performed barium contrast enema may reveal a characteristic colonic filling defect caused by the intussuscepted ileum (Fig. 33-11). Abdominal ultrasonography is quick and reasonably sensitive and specific for detecting intussusceptions (see Fig. 29-8, B). Colonoscopy can be definitive if the intussuscepted intestine is seen extending into the colon (Fig. 33-12). Jejunojejunal intussusceptions may be easier to palpate because of their location. Furthermore, plain abdominal radiographs may be more likely to demonstrate obstructive ileus (i.e., gas-distended bowel loops) because the obstruction is not so far aborad.

A reason for the intussusception (e.g., parasites, mass, enteritis) should always be sought. Fecal examination for parasites and evaluation of full-thickness intestinal biopsy specimens obtained at the time of surgical correction of the intussusception should be performed. In particular, the tip of the intussuscepted bowel (i.e., the intussusceptum) should be examined for a mass lesion (e.g., tumor), which could have served as a focus and allowed the intussusception to occur. Additional diagnostic tests may be warranted depending on the history, physical examination findings, and results of clinical pathologic evaluation.





#### FIG 33-11

B

**A,** Lateral radiograph taken during a barium enema of a dog. Contrast medium outlines the end of a large ileocolic intussusception (thin arrows). Note that barium does not fill up the normally positioned colonic lumen because of a long filling defect (large arrows). **B,** Spot radiograph taken during a barium enema of a dog. The colon is descending on the left (short arrows), and the ileum (long arrows) is entering the colon. There is an area in which barium is displaced, representing an intussuscepted cecum (curved arrows). (**A** courtesy Dr. Alice Wolf, Texas A & M University.)

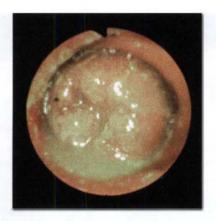


FIG 33-12

Endoscopic view of the ascending colon of a dog with an ileocolic intussusception. Note the large, "hot dog"-like mass in the colonic lumen, which is the intussusception.

#### **Treatment**

Intussusceptions must be treated surgically. Acute ones may be reduced or resected, whereas chronic ones usually must be resected. Recurrence (in the same or a different site) is reasonably common. Surgical plication helps prevent recurrence.

# **Prognosis**

The prognosis is often good if septic peritonitis has not occurred and the intestines do not reintussuscept.

# MISCELLANEOUS INTESTINAL DISEASES

# SHORT BOWEL SYNDROME

# Etiology

Short bowel syndrome occurs when extensive resection of intestines results in the need for special nutritional therapy until the intestines are able to adapt. This is typically an iatrogenic disorder caused by resection of more than 75% to 90% of the small intestine. The remaining intestine is unable to adequately digest and absorb nutrients. Large numbers of bacteria may reach the upper small intestines, especially if the ileocolic valve is removed. However, not all animals with substantial small intestinal resections develop this syndrome. Dogs and cats seem better able than people to tolerate loss of a large percentage of small intestine.

## **Clinical Features**

Affected animals usually have severe weight loss and intractable diarrhea (typically without mucus or blood), which often occurs shortly after eating. Undigested food particles are often seen in the feces.

#### **Diagnosis**

A history of substantial resection in conjunction with the clinical signs is sufficient for diagnosis. It is wise to deter-

mine how much small intestine is left by performing contrast radiographs; estimates made at surgery can be surprisingly inaccurate.

#### **Treatment**

The best treatment is prevention. One should avoid massive resections if at all possible, even if it means doing a "second look" surgery 24 to 48 hours later. If massive resection occurs and the animal cannot maintain its body weight with oral feedings alone, total parenteral nutrition is needed until intestinal adaptation has occurred and treatments have become effective in controlling clinical signs. It is important to continue to feed the animal orally to stimulate intestinal mucosal hypertrophy. The diet should be highly digestible (e.g., low-fat cottage cheese, potato) and should be fed in small amounts, at least three to four times per day. Opiate antidiarrheals (e.g., loperamide), and H2-receptor antagonists may be useful in lessening diarrhea and decreasing gastric hypersecretion. Antibiotics might be needed to control the large bacterial populations now present in the small intestine (pp. 409-410).

## **Prognosis**

If intestinal adaptation occurs, the animal may eventually be fed a near-normal diet. However, some animals will never be able to resume regular diets, and others die despite all efforts. Animals that are initially malnourished seem to have a worse prognosis than those that are well nourished. Some dogs and cats do better than one would intuitively expect them to do, despite the loss of approximately 85% of the small intestines.

#### NEOPLASMS OF THE SMALL INTESTINE

## **ALIMENTARY LYMPHOMA**

#### Etiology

Lymphoma is a neoplastic proliferation of lymphocytes (see Chapter 80) that could also be placed in the section on malabsorptive diseases. It may be caused by FeLV in cats, but the etiology in dogs is unknown. LPE has been suggested to be prelymphomatous in some animals, but the frequency of malignant transformation of LPE to lymphoma is unknown. Lymphoma often affects the intestines, although extraintestinal forms (e.g., lymph nodes, liver, spleen) are more common in dogs (see Chapter 80). Alimentary lymphoma appears to be more common in cats than in dogs.

#### **Clinical Features**

Chronic, progressive weight loss, anorexia, small intestinal diarrhea, and/or vomiting may occur. Alimentary lymphoma may cause nodules, masses, diffuse intestinal thickening resulting from infiltrative disease (see Fig. 29-9), dilated sections of intestine that are not obstructed, and/or focal constrictions. It may also be present in grossly normal-appearing intestine; PLE may also occur. Mesenteric lymph-

adenopathy (i.e., enlargement) is typical but not invariable, and it is important to note that IBD can cause mild to moderate mesenteric lymphadenopathy. Extraintestinal abnormalities (e.g., peripherallymphadenopathy) are inconsistently found in dogs and cats with alimentary lymphoma.

# **Diagnosis**

Diagnosis requires demonstration of neoplastic lymphocytes, which may be obtained by fine-needle aspiration, imprint, or squash cytologic preparations. However, histopathologic evaluation of intestinal biopsy specimens is the most reliable diagnostic method. It is important to biopsy the ileum because many patients (especially cats) do not have lymphoma in the duodenum. If endoscopic biopsy samples are obtained, a poor sample or one that is not sufficiently deep may cause the erroneous diagnosis of LPE instead of lymphoma. Finding lymphocytes in the submucosa is not specific for lymphoma: Lymphocytes can be found in the submucosa of cats with IBD. However, cats with IBD generally do not have the dramatic numbers that can be found in some cases with lymphoma. Occasionally, neoplastic lymphocytes are found only in the serosal layer and fullthickness surgical biopsy specimens are necessary, but this scenario is extremely uncommon. Animals with extremely well-differentiated lymphocytic lymphoma may be impossible to distinguish from those with LPE using routine histopathology, even with multiple full-thickness biopsy samples. This seems to be a particularly important problem in cats. In such cases, diagnosis often depends on finding lymphocytes in organs where they should not be found (e. g., liver) or in performing immunohistochemical studies to determine if the lymphoid population is monoclonal. Paraneoplastic hypercalcemia occasionally occurs but is neither sensitive nor specific for lymphoma.

#### **Treatment**

Chemotherapy is of questionable value in dogs; many patients become quite ill if given aggressive chemotherapy. Cats with well-differentiated small cell lymphoma treated with prednisolone and chlorambucil may do as well as cats with IBD that receive the same therapy. Treatment protocols are outlined in Chapter 80.

# **Prognosis**

The long-term prognosis is very poor, but some cats with well-differentiated intestinal lymphoma will live years with therapy.

# INTESTINAL ADENOCARCINOMA

Intestinal adenocarcinoma is more common in dogs than in cats. It typically causes diffuse intestinal thickening or focal circumferential mass lesions. Primary clinical signs are weight loss and vomiting caused by intestinal obstruction. Diagnosis requires demonstrating neoplastic epithelial cells. Endoscopy, surgery, and ultrasound-guided fine-needle aspiration may be diagnostic. Scirrhous carcinomas have very dense fibrous connective tissue that often cannot be

adequately biopsied with fine-needle aspiration or a flexible endoscope; therefore surgery is sometimes required to obtain diagnostic biopsies. The prognosis is good if com-plete surgical excision is possible, but metastases to regional lymph nodes are common by the time of diagnosis. Postoperative adjuvant chemotherapy does not appear to be beneficial.

# INTESTINAL LEIOMYOMA/ LEIOMYOSARCOMA

Intestinal leiomyomas and leiomyosarcomas are connective tissue tumors that usually form a distinct mass and are primarily found in the small intestine and stomach of older dogs. Primary clinical signs are intestinal hemorrhage, iron deficiency anemia, and obstruction. They can also cause hypoglycemia as a paraneoplastic effect. Diagnosis requires demonstration of neoplastic cells. Evaluation of ultrasound-guided fine-needle aspirate may be diagnostic, but these tumors do not exfoliate as readily as many carcinomas or lymphomas, and biopsy is often necessary. Surgical excision may be curative if there are no metastases. Metastases make the prognosis poor, although some animals are palliated by chemotherapy.

# INFLAMMATION OF THE LARGE INTESTINE

# **ACUTE COLITIS/PROCTITIS**

# Etiology

Acute colitis has many causes (e.g., bacteria, diet, parasites). The underlying cause is seldom diagnosed because this problem tends to be self-limiting. Acute proctitis probably has similar causes but may also be secondary to passage of a rough foreign object that traumatizes the rectal mucosa.

# **Clinical Features**

Animals with acute colitis, which is more common in dogs than in cats, often feel good despite large bowel diarrhea (i.e., hematochezia, fecal mucus, tenesmus). Vomiting occurs infrequently. The major clinical signs of acute proctitis are constipation, tenesmus, hematochezia, dyschezia, and/or depression.

# Diagnosis

Rectal examination is important; animals with acute colitis may have rectal discomfort and/or hematochezia. Eliminating obvious causes (e.g., diet, parasites) and resolving the problem with symptomatic therapy allow the clinician to make a presumptive diagnosis. Colonoscopy and biopsy are definitive but seldom performed or needed unless the initial presentation is unduly severe. Rectal examination of animals with acute proctitis may reveal roughened, thick, and/or obviously ulcerated mucosa. Proctoscopy and rectal mucosal biopsy are definitive but seldom required.

#### **Treatment**

Symptomatic therapy is typically sufficient because acute proctitis and colitis are usually idiopathic. Withholding food for 24 to 36 hours lessens the severity of clinical signs. The animal should then be fed small amounts of a bland diet (e.g., cottage cheese and rice) with or without fiber. After resolution of the clinical signs, the animal may be gradually returned to its original diet. Areas of anal excoriation should be cleansed, and an antibiotic-corticosteroid ointment should be applied. Most animals recover within 1 to 3 days. For proctitis, stool softeners and broad-spectrum antimicrobial therapy effective against anaerobic bacteria may also be used.

# **Prognosis**

The prognosis for idiopathic disease is good.

# **CHRONIC COLITIS**

For a discussion of chronic colitis, see p. 459.

# INTUSSUSCEPTION/PROLAPSE OF THE LARGE INTESTINE

#### **CECOCOLIC INTUSSUSCEPTION**

# **Etiology**

Cecocolic intussusception, in which the cecum intussuscepts into the colon, is rare. The cause is unknown, although some suggest that whipworm-induced typhlitis may be responsible.

# **Clinical Features**

Primarily occurring in dogs, intussuscepted cecums can bleed to the point where some dogs become anemic. Hematochezia is the major sign. It does not lead to intestinal obstruction and infrequently causes diarrhea.

# **Diagnosis**

Cecocolic intussusception is rarely palpated during physical examination. Flexible endoscopy, ultrasonography, and contrast enema (see Fig. 33-11, *B*) usually reveal the intussusception.

#### **Treatment**

Typhlectomy is curative, and the prognosis is good.

# **RECTAL PROLAPSE**

#### Etiology

Rectal prolapse usually occurs secondary to enteritis or colitis in young animals. They begin to strain because of rectal irritation, and eventually some or all of the rectal mucosa prolapses. Mucosal exposure increases irritation and perpetuates straining, which promotes prolapse. Hence a

positive feedback cycle is initiated. Manx cats appear to be predisposed to rectal prolapse.

#### **Clinical Features**

Dogs and cats (especially juveniles) are affected. The presence of colonic or rectal mucosa extending from the anus is obvious during the physical examination.

# **Diagnosis**

The diagnosis is based on physical examination. Rectal examination is needed to differentiate rectal prolapse from an intussusception protruding from the rectum (see p. 465).

#### **Treatment**

Treatment consists of resolving the original cause of straining if possible, repositioning the rectal mucosa, and preventing additional straining/prolapse. A well-lubricated finger is used to reposition the mucosa. If it readily prolapses after being replaced, a purse-string suture in the anus is used for 1 to 3 days to hold it in position. The subsequent rectal opening must be large enough so that the animal can defecate. Occasionally, an epidural anesthetic is needed to prevent repeated prolapse. If the everted mucosa is so irritated that straining continues, retention enemas with kaolin or barium may provide relief. If a massive prolapse is present or the rectal mucosa is irreversibly damaged, resection may be necessary.

## **Prognosis**

The prognosis is usually good, but some cases tend to recur.

#### NEOPLASMS OF THE LARGE INTESTINE

## **ADENOCARCINOMA**

# Etiology

The cause of adenocarcinoma is unknown. Contrary to adenocarcinoma in people, relatively few cases of colonic adenocarcinoma in dogs have been found to arise from polyps. These tumors can extend into the lumen or be infiltrative and produce a circumferential narrowing.

#### **Clinical Features**

Principally found in dogs, colonic and rectal adenocarcinomas are more common in older animals. Hematochezia is common. Infiltrative tumors are likely to cause tenesmus and/or constipation secondary to obstruction.

# **Diagnosis**

Finding carcinoma cells is necessary for a diagnosis. Histopathologic evaluation is often preferable to cytologic analysis because epithelial dysplasia may be present in benign lesions, causing a false-positive cytologic diagnosis of carcinoma. Relatively deep biopsies obtained with rigid biopsy forceps are usually required to diagnose submucosal carcinomas and distinguish benign polyps from carcinomas because invasion of the submucosa is an important feature of rectal adenocarcinomas. Because most colonic neoplasms arise in or near the rectum, digital examination is the best screening test. Colonoscopy is required for masses farther orad. Imaging is used to detect sublumbar lymph node or pulmonary involvement (i.e., metastases).

#### **Treatment**

Complete surgical excision is curative; however, most malignancies cannot be surgically cured because of their location in the pelvic canal, extent of local invasion, and/or tendency to metastasize to regional lymph nodes.

# **Prognosis**

The prognosis for unresectable adenocarcinoma is poor. Preoperative and intraoperative radiotherapy may be palliative for some dogs with nonresectable colorectal adenocarcinomas.

#### **RECTAL POLYPS**

# **Etiology**

The cause of rectal polyps is unknown.

#### **Clinical Features**

Principally found in dogs, hematochezia (which may be considerable) and tenesmus are the primary clinical signs. Obstruction is rare.

# **Diagnosis**

Usually detected during rectal examination, some adenomatous polyps resemble sessile adenocarcinomas because they are so large that the narrow, stalklike attachment cannot be readily discerned. Occasionally, multiple small polyps may be palpated throughout one segment of the colon, usually within a few centimeters of the rectum (Fig. 33-13). Histo-

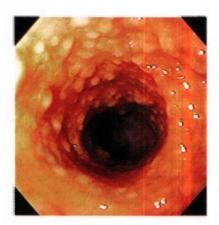


FIG 33-13

Endoscopic view of the distal colon of a dog that has multiple benign polyps. Biopsy is necessary to determine that these are not inflammatory or malignant. pathology is required for diagnosis and to distinguish polyps from malignancies.

#### **Treatment**

Complete excision via surgery or endoscopy is curative. If possible, a thorough endoscopic or imaging evaluation of the colon should be done before surgery to ensure that additional polyps are not present. If they are incompletely excised, polyps return and must be excised again. Multiple polyps within a defined area may necessitate segmental colonic mucosal resection.

# **Prognosis**

Most canine rectal and colonic polyps do not result in carcinoma *in situ*, possibly because they are diagnosed relatively sooner than colonic polyps in people. The prognosis is good.

# MISCELLANEOUS LARGE INTESTINAL DISEASES

# **PYTHIOSIS**

# **Etiology**

As discussed in Chapter 32, pythiosis is caused by *Pythium insidiosum*.

#### **Clinical Features**

Pythiosis of the large bowel usually occurs at or near the rectum. However, it can involve any area of the intestinal tract. Rectal lesions often cause partial obstruction. Fistulae may develop, resembling perianal fistulae. The dog may be presented for constipation and/or hematochezia. Animals

with advanced disease often lose weight. In rare cases there will be infarction of mucosa or vessels with subsequent ischemia. Cats are rarely affected.

# Diagnosis

Because the lesion is submucosal and very fibrotic, rigid biopsy forceps are typically necessary to obtain deep, diagnostic samples that include substantial amounts of submucosa (i.e., where the organism is found; Fig. 33-14). Special stains (e.g., Warthin-Starry) are needed to find the organism. Sometimes, the organism cannot be found, but a suggestive pyogranulomatous, eosinophilic inflammation is present. Serologic tests for antigen and antibodies are available (see Chapter 29).

# **Treatment**

Complete surgical excision is preferred. No medication has consistently been effective, although itraconazole or liposomal amphotericin B plus/minus terbenifine might be temporarily beneficial in some dogs.

# **Prognosis**

The prognosis is poor unless the lesion can be completely excised.

# PERINEAL/PERIANAL DISEASES

## **PERINEAL HERNIA**

# **Etiology**

Perineal hernia occurs when the pelvic diaphragm (i.e., coccygeus and levator ani muscles) weakens and allows the rectal canal to deviate laterally.



#### FIG 33-14

Photomicrograph of a colonic biopsy specimen. The mucosa is intact, but granulomas below the mucosa (arrows) contain fungal hyphae. These granulomas would not be found by superficial mucosal sampling. These granulomas are caused by pythiosis.

#### Clinical Features

This condition is principally found in older intact male dogs (especially Boston Terriers, Boxers, Cardigan Welsh Corgis, and Pekingeses); cats are rarely affected. Most animals present because of dyschezia, constipation, or perineal swelling; however, urinary bladder herniation into this defect may cause severe, potentially fatal postrenal uremia with depression and vomiting.

# Diagnosis

Digital rectal examination should detect rectal deviation, lack of muscular support, and/or a rectal diverticulum. The clinician should check for retroflexion of the urinary bladder into the hernia. If such herniation is suspected, it can be confirmed by ultrasonography, radiographs, catheterizing the bladder, or aspirating the swelling (after imaging) to see if urine is present.

#### Treatment

Animals with postrenal uremia constitute an emergency; the bladder should be emptied and repositioned, and intravenous fluids should be administered. The preferred treatment is surgical reconstruction of the muscular support; however, surgery may fail, and clients should be prepared for the fact that their pet may require additional reconstructive procedures.

# **Prognosis**

The prognosis is fair to guarded.

#### PERIANAL FISTULAE

#### Etiology

The cause of perianal fistulae is unknown. Impacted anal crypts and/or anal sacs have been hypothesized to become infected and rupture into deep tissues. An immune-mediated mechanism is likely to be involved, as seen by the clinical response to immunosuppressive drugs.

#### **Clinical Features**

Perianal fistulae occur in dogs and are more common in breeds with a sloping conformation and/or a broad base to the tail head (e.g., German Shepherd Dogs). There are typically one or more painful draining tracts around the anus. Animals are usually presented because of constipation (caused by the pain), odor, rectal pain, and/or rectal discharge.

# Diagnosis

Diagnosis is made by physical and rectal examination. Care should be taken when examining the patient because the rectal area can be very painful. Draining tracts are sometimes absent, but granulomas and abscesses can be palpated via the rectum. Rectal pythiosis rarely mimics perianal fistulae.

#### **Treatment**

Most affected dogs are cured with immunosuppressive therapy (e.g., cyclosporine, 3 to 5 mg/ kg q12h or azathio-

prine, 50 mg/m² q48h, or topical 0.1% tacrolimus q24h to q12h) with or without antibacterial drugs (e.g., metronidazole, erythromycin). Administering oral ketoconazole (5 mg/kg q12h) may allow a lower dose of cyclosporine to be effective, thus decreasing the client's cost. If cyclosporine is used, the clinician should monitor therapeutic blood levels of the drug to ensure that adequate blood levels are present. Hypoallergenic diets may also be beneficial. Rarely, animals will not respond to medical therapy and will require surgery. Surgery may cause fecal incontinence. Postoperative care is important and consists of keeping the area clean. Fecal softeners are sometimes useful.

# **Prognosis**

Many patients are treated successfully. However, the prognosis is guarded, and repeated medical care or surgeries may be needed.

# **ANAL SACCULITIS**

# Etiology

In anal sacculitis the anal sac becomes infected, resulting in an abscess or cellulitis.

#### **Clinical Features**

Anal sacculitis is relatively common in dogs and occasionally occurs in cats. Small dogs (e.g., Poodles, Chihuahuas) probably have a higher incidence of this disorder than other breeds. Mild cases cause irritation (i.e., scooting, licking, or biting the area). Anal sacs occasionally bleed onto the feces. Severe cases may be associated with obvious pain, swelling, and/or draining tracts. Dyschezia or constipation may develop because the animal refuses to defecate. Fever may occur in dogs and cats with severe anal sacculitis.

# Diagnosis

Physical and rectal examination is usually diagnostic. The anal sacs are often painful; the sac contents may appear purulent, bloody, or normal but increased in volume. In severe cases it may be impossible to express the affected sac. If the sac ruptures, the fistulous tract is usually in a 4 o'clock or 7 o'clock position in relation to the anus. Occasionally, there is an obvious abscess.

#### **Treatment**

Mild cases require only that the anal sac be expressed and an aqueous antibiotic-corticosteroid preparation be infused. Infusion with saline solution may aid in expressing impacted sacs. If clients express the anal sacs at home, they can often prevent impaction and reduce the likelihood of severe complications.

Abscesses should be lanced, drained, flushed, and treated with a hot pack; systemic antibiotics should also be administered. Hot packs also help soft spots form in early abscesses. If the problem recurs, is severe, or is nonresponsive to medical therapy, affected sacs can be resected.

# **Prognosis**

The prognosis is usually good.

# PERIANAL NEOPLASMS

# ANAL SAC (APOCRINE GLAND) ADENOCARCINOMA

# **Etiology**

Anal sac adenocarcinomas are derived from the apocrine glands and are usually found in older female dogs.

#### **Clinical Features**

An anal sac or pararectal mass can often be palpated, but some are not obvious. Paraneoplastic hypercalcemia causing anorexia, weight loss, vomiting, and polyuria-polydipsia is common. Occasionally, constipation occurs as a result of the hypercalcemia or perineal mass. Metastatic sublumbar lymphadenopathy occurs early in the course of the disease, but metastases to other organs are rare.

# Diagnosis

Cytologic and/or histopathologic evaluation is necessary to establish a diagnosis. Hypercalcemia in an older female dog should lead to careful examination of both anal sacs and pararectal structures. Abdominal ultrasonography may reveal sublumbar lymphadenopathy.

#### **Treatment**

Hypercalcemia, if present, must be treated (see Chapter 55). The tumor should be removed, but these tumors have often metastasized to regional lymph nodes by the time of diagnosis. Palliative chemotherapy (see Chapter 77) may be transiently beneficial in some dogs.

# **Prognosis**

The prognosis is guarded.

# **PERIANAL GLAND TUMORS**

#### Etiology

Perianal gland tumors arise from modified sebaceous glands. Perianal gland adenomas have testosterone receptors.

#### **Clinical Features**

Perianal gland adenomas are often sharply demarcated, raised, and red and may be pruritic. Commonly found around the anus and base of the tail, they may be solitary or multiple and can occur over the entire back half of the dog. Male hormones appear to stimulate their growth, and they are often found in older intact male dogs (especially Cocker Spaniels, Beagles, and German Shepherd Dogs). Pruritus may lead to licking and ulceration of the tumor. Perianal gland adenocarcinomas are rare; they are usually large, infiltrative, ulcerated masses with a high metastatic potential.

# Diagnosis

Cytologic and/or histopathologic evaluation is needed for diagnosis, but neither reliably distinguishes malignant from benign masses. Finding metastases (e.g., regional lymph nodes, lungs) is the most certain method of diagnosing malignancy.

#### **Treatment**

Surgical excision is preferred for benign or solitary tumors that have not metastasized. Neutering is recommended for dogs with adenomas. Radiation is recommended for multicentric and some malignant tumors. Chemotherapy (vincristine, adriamycin, cyclophosphamide [VAC] protocol) is helpful in dogs with adenocarcinomas (see Chapter 77).

# **Prognosis**

The prognosis is good for benign lesions but guarded for malignant lesions.

# CONSTIPATION

Constipation may be caused by any perineal or perianal disease that causes pain (e.g., perianal fistulae, perineal hernia, anal sacculitis), obstruction, or colonic weakness. It may also be caused by other disorders (see Box 28-15).

# PELVIC CANAL OBSTRUCTION CAUSED BY MALALIGNED HEALING OF OLD PELVIC FRACTURES

# Etiology

Prior trauma (e.g., automobile-associated injuries) is a common cause of pelvic canal obstruction in cats because they frequently sustain pelvic trauma that heals if they are allowed to rest. Cats appear clinically normal once the fractures heal, but the diminution of the pelvic canal can produce megacolon and/or dystocia.

## Diagnosis

Digital rectal examination should be diagnostic. Radiographs will further define the extent of the problem.

# **Treatment**

Constipation caused by minimal pelvic narrowing may be controlled with stool softeners, but orthopedic surgery may be needed. The prognosis depends somewhat on how severely the colon has been distended. Unless the colon is massively stretched out of shape, it can often resume function if it is kept empty and allowed to regain its normal diameter. Prokinetic drugs such as cisapride (0.25 mg/kg administered orally q8-12h) may stimulate peristalsis; however, prokinetic drugs must not be used if there is residual obstruction.

#### **Prognosis**

The prognosis depends on the severity and chronicity of colonic distention and the success of surgery in widening the pelvic canal.

# BENIGN RECTAL STRICTURE

# Etiology

The cause is uncertain but may be congenital.

#### Clinical Features

Constipation and tenesmus are the principal clinical signs.

# Diagnosis

Digital rectal examination detects a stricture, although this sign can be missed if a large dog is palpated carelessly or if the stricture is beyond reach. Proctoscopy and evaluation of a deep biopsy specimen (i.e., including submucosa) of the stricture are needed to confirm that the lesion is benign and fibrous as opposed to neoplastic or fungal.

#### **Treatment**

In some animals, simple dilation via balloon or retractor will tear the stricture and allow normal defecation; other animals require surgery. Owners should be warned that strictures may re-form during healing, and surgery can cause incontinence in rare cases. Corticosteroids (prednisolone, 1.1 mg/ kg/day) might impede stricture re-formation.

# Prognosis

The prognosis is guarded to good.

# DIETARY INDISCRETION LEADING TO CONSTIPATION

Etiology Dogs often eat inappropriate foods or other materials (e.g., paper, popcorn, hair, bones). Excessive dietary fiber supplements can cause constipation if the animal becomes dehydrated.

# Diagnosis

Dietary causes are common in dogs that eat trash. Dietary indiscretion is best diagnosed by examining fecal matter retrieved from the colon.

## Treatment

Controlling the pet's eating habits, adding appropriate amounts of fiber to the diet, and feeding a moist diet (especially in cats) help prevent constipation. Repeated retention and cleansing (not hypertonic) enemas may be needed. Manual disruption of hard feces should be avoided, but if it is necessary, the animal should be anesthetized to help prevent colonic trauma during the procedure, and sponge forceps or curved hemostats should be used to mechanically break apart the feces. It often helps to insert a rigid colonoscope up to the fecal mass and then insert a tube with a vigorous stream of running water at body temperature issuing from the tip. This will soften the fecal mass and wash away debris that breaks off.

# **Prognosis**

The prognosis is usually good. The colon should function normally after cleansing unless the distention has been prolonged and severe.

# IDIOPATHIC MEGACOLON

The cause is unknown but may involve behavior (i.e., refusal to defecate) or altered colonic neurotransmitters.

# Clinical Features

Idiopathic megacolon is principally a feline disease, although dogs are occasionally affected. Affected animals may be depressed and anorectic and are often presented because of infrequent defecation.

# Diagnosis

Diagnosis requires palpating a massively dilated colon (not one just filled to normal capacity) plus elimination of dietary, behavioral, metabolic, and anatomic causes. Abdominal radiographs should be evaluated if proper abdominal palpation cannot be performed.

#### Treatment

Impacted feces must be removed. Multiple warm water retention and cleansing enemas over 2 to 4 days usually work. Future fecal impaction is prevented by adding fiber to a moist diet (e.g., Metamucil, pumpkin pie filling), making sure clean litter is always available, and using osmotic laxatives (e.g., lactulose) and/or prokinetic drugs (e.g., cisapride). Lubricants are not helpful, because they do not change fecal consistency. If this conservative therapy fails or is refused by the client, subtotal colectomy is indicated in cats (not dogs). Cats typically have soft stools for a few weeks postoperatively, some for the rest of their lives.

#### **Prognosis**

The prognosis is fair to guarded. Many cats respond well to conservative therapy if treated early.

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# CHAPTER Disorders of the Peritoneum

# CHAPTER OUTLINE

INFLAMMATORY DISEASES

Septic Peritonitis
Sclerosing, Encapsulating Peritonitis
HEMOABDOMEN

Abdominal Hemangiosarcoma
MISCELLANEOUS PERITONEAL DISORDERS

Abdominal Carcinomatosis Mesothelioma Feline Infectious Peritonitis

# **INFLAMMATORY DISEASES**

# SEPTIC PERITONITIS

#### Etiology

Spontaneous septic peritonitis is usually caused by alimentary tract perforation or devitalization caused by neoplasia, ulceration, intussusception, foreign objects, or dehiscence of suture lines. Septic peritonitis can also develop after abdominal gunshot wounds, surgery, or hematogenous spread from elsewhere. Cats seemingly can develop spontaneous septic peritonitis.

#### **Clinical Features**

If septic peritonitis occurs secondary to suture line dehiscence, it classically manifests 3 to 6 days postoperatively. Dogs with two or more of the following have been reported to be at increased risk for dehiscence: serum albumin <2.5 g/dl, intestinal foreign body, and preoperative peritonitis. Dogs with septic peritonitis are usually depressed, febrile, and vomiting and may have abdominal pain (if they are not too depressed to respond). Abdominal effusion is usually mild to modest in amount. Signs usually progress rapidly until septic shock (i.e., systemic inflammatory response syn-

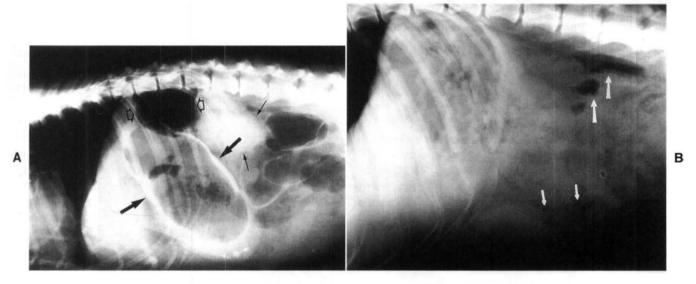
drome [SIRS]) occurs. However, some animals with septic peritonitis may have mild vomiting, slight fever, and copious volumes of abdominal fluid and feel relatively well for days or longer. In particular, cats with septic peritonitis may not show signs of abdominal pain and may be bradycardic.

# Diagnosis

Most animals with septic peritonitis have small amounts of abdominal fluid that cannot be detected by physical examination but that decrease serosal detail on plain abdominal radiographs (much like what is seen in animals with a lack of body fat). Ultrasonography is a sensitive means for detecting such small fluid volumes. Free peritoneal gas not related to recent abdominal surgery strongly suggests alimentary tract leakage (Fig. 34-1) or infection with gas-forming bacteria. Ultrasonography may detect masses (e.g., tumors) responsible for such leakage. Neutrophilia is common but nonspecific in dogs and cats with septic peritonitis.

Abdominocentesis is indicated if free abdominal fluid is detected or if septic peritonitis is suspected. Retrieved fluid is examined cytologically and cultured. Ultrasound guidance should allow the clinician to sample effusions, even when only minimal amounts are present.

Bacteria (especially if phagocytized by white blood cells) or fecal contents in abdominal fluid are diagnostic for septic peritonitis (Fig. 34-2). However, fecal contents and bacteria are often not seen despite severe infection. Prior antibiotic use may greatly suppress bacterial numbers and the percentage of neutrophils demonstrating degenerative changes. Furthermore, mild degenerative changes are common after recent abdominal surgery. More important, it is almost impossible to quickly distinguish septic peritonitis from sterile pancreatitis in some dogs without exploratory laparotomy. Both can cause SIRS, and ultrasound is not as sensitive in detecting pancreatitis as desired. Effusion lactate levels are not accurate in distinguishing septic from nonseptic effusions. Degenerative neutrophils are suggestive of septic peritonitis, but severe sterile pancreatitis can produce degenerative changes identical to that seen with infection. Unfor-



A, Plain lateral abdominal radiograph of a dog. Visceral margins of kidney (small solid arrows) and stomach (large solid arrows) are outlined by negative contrast (i.e., air). In addition, there are pockets of free air in the abdomen (open arrows). This dog had a gastric ulcer that spontaneously perforated. B, Plain lateral radiograph of a dog with a splenic abscess. There are air bubbles in the region of the spleen (short arrows) and free gas in the dorsal peritoneal cavity (long arrows).

tunately, when septic peritonitis is strongly suspected, the clinician typically cannot wait for results of abdominal fluid culture. At this time, the ability of canine pancreatic lipase-immunoreactivity determinations to discriminate between the two is uncertain, especially since dogs with septic peritonitis may have secondary pancreatitis if the intestinal perforation is close to the pancreas. Therefore the clinician should always warn the client that the patient may or may not need the procedure but that there is no quick, reliable way to distinguish before surgery.

# **Treatment**

Animals with spontaneous septic peritonitis usually have an alimentary tract leak and should be surgically explored as soon as they are stable. A preanesthetic complete blood count (CBC), serum biochemistry profile, and urinalysis are desirable; however, surgery usually should not be delayed even if the laboratory results are. During surgery a careful search should be made for intestinal or gastric defects. Biopsy of tissue surrounding a perforation should be performed to search for underlying neoplasia or inflammatory bowel disease (IBD). After the defect is corrected, the abdomen should be repeatedly lavaged with large volumes of warm crystalloid solutions to dilute and remove debris and bacteria. The abdomen cannot be adequately lavaged via a drain tube or even a peritoneal dialysis catheter except in the mildest cases. Adhesions re-form quickly; they should not be broken down unless it is necessary to examine the intestines. Intestines should be resected only if they are truly devitalized. Intestines are sometimes unnecessarily removed because of adhesions, resulting in short bowel syndrome (see p. 466), which has substantial morbidity.

Substantial abdominal contamination may require protracted drainage. Penrose drains are typically inadequate for this purpose. Open abdominal drainage may be done, but it is very time and labor intensive. A nonabsorbable suture is used to close the abdomen except for a 6- to 8-cm opening at its most dependent aspect. This open incision is covered with sterile absorbent dressings (e.g., a sterile sanitary napkin held in place by sterile cast padding and sterile gauze) that are changed as needed, usually two to four times per day initially. Eventually, only one change per day will be needed. When the dressing is changed, a sterile, gloved hand should explore the opening to ensure that omentum and intestines have not blocked the site. This dressing change regimen is continued until abdominal drainage decreases and most or all of the peritoneal contamination is gone. Then a second surgery is performed to close the abdomen. The opening sometimes closes spontaneously. The abdomen should be recultured at the time of the second surgery. Alternatively, closed suction drains have been used postoperatively with success, and some clinicians advocate closure of such abdomens without drainage.

Systemic antimicrobial therapy should consist of broad-spectrum, parenteral antibiotics. A combination of a plactam drug (e.g., ticarcillin plus clavulinic acid) and metronidazole plus an aminoglycoside (e.g., amikacin) is usually an excellent choice (see the discussion of antibacterial drugs used in gastrointestinal disorders, p. 409). Enrofloxacin may be substituted for the aminoglycoside, but it must be

**FIG 34-2 A,** Photomicrograph of peritoneal exudate from a dog with septic peritonitis. Note bacteria (small arrows) and neutrophils that have degenerated so much that it is difficult to identify them as neutrophils (large arrows). (Wright's stain; magnification ×1000.) (Courtesy Dr. Claudia Barton, Texas A & M University.) **B,** Photomicrograph of septic peritoneal fluid. There is one intracellular bacterium (large arrow) and two things (small, clear arrows) that may or may not be bacteria. The neutrophils are not nearly as degenerated as in **A**.

given over 30 to 40 minutes in a diluted form. Aminoglycosides and quinolones are dose-dependent drugs; administration of the entire daily dose in one injection is safer and probably as or more effective than administering smaller doses two to three times daily. Cefoxitin (30 mg/kg q6-8h) and meropenem (24 mg/kg once daily) are other  $\beta$ -lactam drugs that may be used. Fluid and electrolyte support helps prevent aminoglycoside-induced nephrotoxicity. Hypoalbuminemia can occur, especially if open abdominal drainage is used. If disseminated intravascular coagulation (DIC) is present, administration of fresh frozen plasma to replenish antithrombin III (AT III) and other clotting

factors is optimal; plasma is given until the AT III concentration and the prothrombine time (PT) and partial thromboplastin time (PTT) are normal or clearly much improved. Heparin may also be administered; low molecular weight heparin is believed to be more effective than unfractionated heparin.

#### **Prognosis**

The prognosis depends on the cause of the leak (e.g., perforations may be caused by malignancies) and the animal's condition when it is diagnosed. SIRS and DIC worsen the prognosis.

## SCLEROSING, ENCAPSULATING PERITONITIS

#### Etiology

Reported causes include bacterial infection, steatitis, and fiberglass ingestion. This form of peritonitis is rare.

#### **Clinical features**

Sclerosing, encapsulating peritonitis is a chronic condition in which abdominal organs are covered and encased in heavy layers of connective tissue. Typical clinical signs usually include vomiting, abdominal pain, and ascites. During exploratory surgery the lesions may mimic those of a mesothelioma. Analysis of abdominal fluid usually reveals red blood cells, mixed inflammatory cells, and macrophages. Diagnosis is confirmed by surgical biopsy of the thick covering of the abdominal organs.

#### Treatment

Antibiotics with or without corticosteroids may be tried. Removal of underlying causes (e.g., steatitis in cats) is desirable, but such causes are rarely found.

#### **Prognosis**

Most affected animals die despite therapeutic attempts.

#### **HEMOABDOMEN**

Most red effusions are blood-tinged transudates, not hemoabdomen. Hemoabdomen is usually indicated by a fluid with a hematocrit greater than or equal to 10% to 15%. Blood in the abdominal cavity can be iatrogenic (i.e., caused by abdominocentesis), traumatic (e.g., automobile-associated trauma), or toxic (e.g., ingestion of vitamin K antagonist) in origin, or can represent spontaneous disease. Clots or platelets in the sample mean that the bleeding is iatrogenic or is currently occurring near the site of the abdominocentesis. Spontaneous hemoabdomen is usually the result of a bleeding neoplasm (e.g., hemangiosarcoma, hepatocellular carcinoma). History, physical examination, coagulation studies, and/or abdominal ultrasonography usually establish the diagnosis. It should be noted that thrombocytopenia may cause or be caused by vigorous abdominal bleeding. Also, even when a coagulopathy is secondary to the original cause of the hemoabdomen (e.g., tumor), it may become severe enough to cause bleeding by itself.

#### ABDOMINAL HEMANGIOSARCOMA

#### Etiology

Abdominal hemangiosarcoma often originates in the spleen (see Chapter 82). It can spread throughout the abdomen by implantation, causing widespread peritoneal seepage of blood, or it can metastasize to distant sites (e.g., liver, lungs).

#### Clinical features

Abdominal hemangiosarcoma is principally found in older dogs, especially German Shepherd Dogs and Golden Retrievers. Anemia, abdominal effusion, and periodic weakness or collapse from poor peripheral perfusion are common presenting complaints. Some animals have bicavity hemorrhagic effusion.

#### Diagnosis

Ultrasonography is the most sensitive test for splenic and hepatic masses, especially when there is copious abdominal effusion. Radiographs may reveal a mass if there is minimal free peritoneal fluid. Abdominocentesis typically reveals hemoabdomen but not neoplastic cells. Definitive diagnosis requires biopsy (via laparotomy) because splenic hematoma, hemangioma, and widespread accessory splenic tissue masquerade as hemangiosarcoma but have a much better prognosis. Two or more large tissue samples should always be submitted, and the clinician should be prepared to request recuts; hemangiosarcoma may be difficult to find histologically. Fine-needle biopsy (especially fine-needle core biopsy) is sometimes diagnostic. However, there is the risk of inducing life-threatening hemorrhage, and the patient must be watched closely after the procedure for evidence of hypovolemia.

#### **Treatment**

Solitary masses should be excised. Chemotherapy may be palliative for some animals with multiple masses; chemotherapy is also indicated as an adjuvant postoperative treatment modality (see Chapter 82).

#### **Prognosis**

The prognosis is poor because the tumor metastasizes early.

## MISCELLANEOUS PERITONEAL DISORDERS

#### **ABDOMINAL CARCINOMATOSIS**

#### Etiology

Abdominal carcinomatosis involves widespread, miliary peritoneal carcinomas that may have originated from various sites; intestinal and pancreatic adenocarcinomas are common neoplasms that may result in carcinomatosis.

#### **Clinical Features**

Weight loss may be the predominant complaint, although some animals are presented because of obvious abdominal effusion.

#### Diagnosis

Physical examination and radiography rarely help to establish the diagnosis. Ultrasonography may reveal masses or infiltrates if they are large enough; however, small, miliary lesions can be missed by ultrasound. Fluid analysis reveals a nonseptic exudate or a modified transudate; epithelial neo-

plastic cells are occasionally found (see Chapter 36). Laparoscopy or abdominal exploratory surgery with histologic examination of biopsy specimens is usually needed for diagnosis.

#### **Treatment**

Intracavitary chemotherapy has been palliative for some animals, although generally there is no effective treatment for this disorder. Cisplatin (50 to 70 mg/m² every 3 weeks) and 5-fluorouracil (150 mg/m² every 2 to 3 weeks) are frequently effective in decreasing fluid accumulation in dogs with carcinomatosis but should not be used in cats; carboplatin (150 to 200 mg/m² every 3 weeks) may be effective in cats.

#### **Prognosis**

The prognosis is grim.

#### MESOTHELIOMA

#### Etiology

The cause is unknown.

#### **Clinical Features**

Mesothelioma often causes bicavity effusion. The tumor may appear as fragile clots adhering to the peritoneal surface of various organs.

#### Diagnosis

Imaging reveals only fluid accumulations. Fluid cytology rarely is beneficial because reactive mesothelial cells are notorious for mimicing malignancy, and pathologists generally acknowledge the inability to cytologically distinguish neoplastic cells from nonneoplastic cells in abdominal fluid. Laparoscopy or laparotomy are typically needed to make a definitive diagnosis.

#### **Treatment**

Intracavity cis-platinum may be attempted.

#### **Prognosis**

The prognosis is grim, but chemotherapy has been reported to prolong survival by several months.

#### **FELINE INFECTIOUS PERITONITIS**

Feline infectious peritonitis (FIP) is a viral disease of cats, which is discussed in detail in Chapter 97. Only the abdom-

inal effusion of FIP is discussed here. Although a major cause of feline abdominal effusion, FIP is not the only cause. Furthermore, not all cats with FIP have effusions. FIP effusions are classically pyogranulomatous (i.e., macrophages and nondegenerate neutrophils) with a relatively low nucleated cell count (i.e.,  $\leq 10,000/\mu$ l). However, some cats with FIP have effusions that primarily contain neutrophils. A nonseptic exudate in a nonazotemic cat suggests FIP until proven otherwise.

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- Sharpe A et al: Intestinal haemangiosarcoma in the cat: clinical and pathological features of four cases, *J Small Anim Pract* 41:411, 2000
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GENERIC NAME	TRADE NAME DOSE FOR DOGS		DOSE FOR CATS	
Albendazole	Valbazen	25 mg/kg PO q12h for 3 days	Same for 5 days	
Aluminum hydroxide	Amphojel	10-30 mg/kg; PO q6-8h	Unknown	
Amikacin	Amiglyde	20-25 mg/kg IV q24h	Same	
Aminopentamide Amoxicillin	Centrine	0.01-0.03 mg/kg PO, IV, SC q8-12h 22 mg/kg PO, IM, SC, q12h	0.02 mg/kg PO, SC q8-12h Same	
Amphotericin B	Fungizone	0.1-0.5 mg/kg IV q2-3d; watch for toxicity	0.1-0.3 mg/kg IV q2-3d; watch for toxicity	
Amphotericin B, lipid complex or liposomal	Abelcet AmBisome	1.1-3.3 mg/kg/treatment IV; watch for toxicity	0.5-2.2 mg/kg/treatment IV; not approved watch for toxicity	
Ampicillin		22 mg/kg IV, q6-8h	Same	
Amprolium		25 mg/kg (puppies) for 3-5 days (not approved)	Do not use	
Apomorphine Atropine		0.02-0.04 mg/kg IV; 0.04-0.1 mg/kg SC 0.02-0.04 mg/kg IV, SC q6-8h; 0.2-0.5 mg/kg IV, IM for organophosphate toxicity	Do not use Same	
Azathioprine	lmuran	50 mg/m <sup>2</sup> PO q24-48h (not approved)	Do not use in cats	
Azithromycin	Zithromax	10 mg/kg PO q12-24h (not approved)	5-15 mg/kg PO q24h (not approved)	
Bethanechol	Urecholine	1.25-15 mg total dose PO q8h	1.2-5 mg total dose PO	
Bisacodyl	Dulcolax	5-15 mg total dose PO as needed	5 mg total dose PO q24h	
Bismuth subsalicylate	Pepto-Bismol	1 ml/kg/day PO divided q8-12h for 1-2 days	Do not use	
Budesonide	Entocort	1-3 mg/dog PO q24-48h (not approved)	1 mg/cat PO q24-72h (not approved)	
Butorphanol	Torbutrol, Torbugesic	0.2-0.4 mg/kg IV, SC, IM q2-3h as needed	0.2 mg/kg IV, SC as needed	
Cefazolin	Ancef	20-25 mg/kg IV, IM, SC q6-8h	Same	
Cefotaxime	Claforan	20-80 mg/kg IV, IM, SC q6-8h (not approved)	Same (not approved)	
Cefoxitin Chlorambucil	Mefoxin Leukeran	30 mg/kg IV, IM, SC q6-8h (not approved) Not used for IBD	Same as dogs (not approved)	
Chlordinbuch	Leukeran	NOT used for IDD	1 mg twice weekly for cats <3.5 kg; 2 mg twice weekly for cats >3.5 kg (not approved)	
Chloramphenicol		50 mg/kg PO, IV, SC q8h	Same, but q12h	
Chlorpromazine	Thorazine	0.3-0.5 mg/kg IV, IM, SC q8-12h for vomiting	Same	
Cimetidine	Tagamet	5-10 mg/kg PO, IV, SC <b>qó-</b> 8h	Same	
Cisapride	Propulsid	0.25-0.5 mg/kg PO q8-12h	2.5-5 mg total dose PO q8-12h (1 mg/kg maximum dose)	
Clindamycin	Antirobe	11 mg/kg PO q8h	Same	
Cyclosporine	Atopica	3-5 mg/kg PO q12h	Not for use in cats	
Cyproheptadine	Periactin	Not used for anorexia in dogs	2-4 mg total dose	
Dexamethasone	Azium	0.05-0.1 mg/kg IV, SC, PO q24h for inflammation	Same	
Diazepam	Valium	Not for use in anorexic dogs	0.2 mg IV	
Dicyclomine	Bentyl	0.15 mg/kg PO q8h	Unknown	
Dioctyl sodium sulfosuccinate	Colace	10-200 mg total dose PO, depending on weight, q8-12h	10-25 mg total dose PO q12-24h	
Diphenhydramine	Benadryl	2-4 mg/kg PO; 1-2 mg/kg IV, IM q8-12h	Same	
Diphenoxylate	Lomotil	0.05-0.2 mg/kg PO q8-12h	Do not use	
Dolasetron	Anzemet	0.3-1.0 mg/kg SC or IV q24h (not approved)	Same (not approved)	
Doxycycline	Vibramycin	10 mg/kg PO q24h or 5 mg/kg PO q12h	5-10 mg/kg PO q12h	



#### Drugs Used in Gastrointestinal Disorders—cont'd

GENERIC NAME	TRADE NAME	DOSE FOR DOGS	DOSE FOR CATS		
Enrofloxacin	oxacin Baytril 2.5-20 mg/kg PO or IV (diluted) q12-24h		Same (high doses can be associated with blindness)		
Episprantel	Cestex	5.5 mg/kg PO once	2.75 mg/kg PO once		
Erythromycin		11-22 mg/kg PO q8h (for antimicrobial action); 2 mg/kg PO q8-12h (for prokinetic activity)	Same		
Famotidine	Pepcid	0.5 mg/kg PO, IV q12-24h (higher doses may be necessary in severely stressed dogs)	Same (not approved)		
Febantel		10 mg/kg PO q24h for 3 days (adult dogs) 15 mg/kg PO q24h for 3 days (puppies)	10 mg/kg PO q24h		
Febantel plus pyrantel plus praziquantel	Drontal plus	See manufacturer's recommendations	Not approved		
Fenbendazole	Panacur	50 mg/kg PO q24h for 3-5 days	Not approved, but probably the same as for dogs		
Flunixin meglumine	Banamine	1 mg/kg IV for septic shock (controversial)	Not recommended		
Furazolidone	Furoxone	4.4 mg/kg PO q12h for 5 days for giardiasis	Same		
Granisetron	Kytril	0.1-0.5 mg/kg PO (not approved)			
Hetastarch		10-20 mk/kg/day	10-15 mg/kg/day		
Imidocloprid/ moxidectin	Advantage multi	See manufacturer's recommendations	Same		
Imipenem-Cilastatin	Primaxin	5 mg/kg IV, IM, SC q4-6h (not approved)	Same (not approved)		
nterferon-ώ	Virbagen Omega	2,500,000 units/kg IV, SQ q24h	1,000,000 units/kg SC q24h		
traconazole	Sporanox	5 mg/kg PO q12h (not approved)	Same (not approved)		
lvermectin		200 µg/kg PO (not in Collies or other sensitive breeds) for intestinal parasites	250 μg/kg PO		
Kaopectate		1-2 ml/kg PO q8-12h	Not recommended		
Ketamine		Not used	1-2 mg/kg IV for 5-10 minutes of restraint		
Ketoconazole	Nizoral	10-20 mg/kg PO q24h (not approved)	Same (usually divided dose)		
Lactulose	Cephulac	0.2 ml/kg P○ q8-12h, then adjust (not approved)	5 ml PO q8h (not approved)		
Lanosprazole	Prevacid	1 mg/kg IV q24h (not approved)	Unknown		
Loperamide	Imodium	0.1-0.2 mg/kg PO q8-12h (not approved)	0.08-0.16 mg/kg PO q12h (not approved)		
Magnesium hydroxide	Milk of Magnesia	5-10 ml total dose PO q6-8h (antacid)	5-10 ml total dose PO q8-12h (antacid)		
Maropitant	Cerenia	1 mg/kg SC or 2 mg/kg PO q24h	Not approved		
Megestrol acetate	Ovaban	0.25-0.5 mg/kg PO q24h (dogs) (not recommended)	2.5-5 mg/cat PO q24h (not recommended)		
Meropenem	Merrem IV	12 mg/kg SC q8-12h or 24 mg/kg IV q24h (not approved)	Same (not approved)		
Mertazapine	Remeron	3.75 to 22.5 mg PO daily, depending upon size (anecdotal and not approved)	3.75 mg PO q48-72h (anecdoto and not approved)		
Mesalamine	Pentasa	10-20 mg/kg PO q12h (not approved)	Not recommended		
Methscopolamine Methylprednisolone	Pamine Depo-Medrol	0.3-1 mg/kg PO q8h 1 mg/kg IM q1-3 wk	Unknown 10-40 mg total dose IM q1-3 wk		
acetate Metoclopramide	Reglan	0.25-0.5 mg/kg IV, PO, IM q8-24h	Same (not approved)		
Metronidazole	Flagyl	1-2 mg/kg/day, CRI 25-50 mg/kg PO q24h for 5-7 days for giardiasis; 10-15 mg/kg PO q12-24h for	25-50 mg/kg PO q24h for 5 do for giardiasis; 10-15 mg/kg P		

## Drugs Used in Gastrointestinal Disorders—con

GENERIC NAME	TRADE NAME	DOSE FOR DOGS	DOSE FOR CATS	
Milbemycin	Interceptor	0.5 mg/kg PO monthly	Not approved	
Misoprostol	Cytotec	2-5 µg/kg PO q8h (not approved)	Unknown	
Neomycin	Biosol	10-15 mg/kg PO q6-12h	Same	
Nizatidine	Axid	2.5-5 mg/kg PO q24h (not approved)	Unknown	
		2.3-3 hig/kg PO q24h (not approved)		
Olsalazine	Dipentum	10 mg/kg PO q12h (not approved)	Unknown	
Omeprazole	Prilosec	0.7-1.5 mg/kg PO q12-24h (not approved)	Same (not approved)	
Ondansetron	Zofran	0.5-1 mg/kg PO; 0.1-0.2 mg/kg IV q8-24h (not approved)	Unknown	
Orbifloxacin	Orbax	2.5-7.5 mg/kg PO q24h	Same	
Oxazepam	Serax	Not used for anorexia	2.5 mg total dose PO	
Oxytetracycline		22 mg/kg PO q12h	Same	
Pancreatic	Viokase V	1-3 tsp/454 g of food	Same	
enzymes	Pancreazyme			
Pantoprazole	Protonix	1 mg/kg IV q24h (not approved)	Unknown	
Paregoric	Corrective	0.05 mg/kg PO q12h (not approved)	Not recommended	
	mixture			
Piperazine	5 .	44-66 mg/kg PO once	Same	
Praziquantel	Droncit	See manufacturer's recommendations	See manufacturer's recommendations	
Prednisalone		1.1-2.2 mg/kg PO, IV, SC, q24h or	Same	
		divided, for antiinflammatory effects		
Prochlorperazine	Compazine	0.1-0.5 mg/kg IM q8-12h	0.13 mg/kg IM q12h (not approved)	
Propantheline	Pro-Banthine	0.25-0.5 mg/kg PO q8-12h (not approved)	Same (not approved)	
Psyllium hydrocolloid	Metamucil	1-2 tsp/454 g of food	Same	
Pyrantel pamoate	Nemex	5 mg/kg PO	20 mg/kg PO	
Pyridostigmine	Mestinon	0.5-2 mg/kg PO q8-12h	Not used	
Rantidine	Zantac	1-2 mg/kg PO, IV, IM, q8-12h (not approved)	2.5 mg/kg IV; 3.5 mg/kg PO q12h	
Ronidazole		unknown	30-50 mg/kg q12h PO for 14 days (not approved)	
Selemectin	Revolution	6 mg/kg topically (not approved)	6 mg/kg topical	
Sucralfate	Carafate	0.5-1 g qó-8h, depending on size	0.25 g q6-12h	
Sulfadimethoxine	Albon	50 mg/kg PO first day, then 27.5 mg/kg PO q12h for 9 days	Same	
Sulfasalazine	Azulfidine	10-20 mg/kg PO q6-8h, not to exceed 3 q/day	Not recommended, but 7.5 mg/kg PO q12h is used	
Tegaserod	Zelnorm	0.05-0.10 mg/kg PO q12h	Unknown	
Tetracycline	261101111	22 mg/kg PO q8-12h	Same	
Thiabendazole	Omnizole	50 mg/kg PO q24h for 3 days (not	Unknown	
Ticarcillin plus clavulinic acid	Timentin	approved) 50 mg/kg IV q6-8h (not approved)	40 mg/kg IV q6-8h (not approved)	
Toltrazuril	Ваусох	5-20 mg/kg PO q24h (dogs)	Unknown (cats)	
Trimethobenzamide	Tigan	3 mg/kg IM q8h (not approved)	Unknown	
Trimethoprim- sulfadiazine	Tribrissen, Bactrim	30 mg/kg PO q24h for 10 days	Same as for dogs	
Tylosin	Tylan	20-40 mg/kg PO q12-24h in food	Same	
Vitamin B <sub>12</sub>	ryioni	100-200 mg PO q24h or 0.25-1.0 mg IM, SC q7d (dogs)	50-100 mg PO q24h (cats) or 0.15-0.25 mg IM, SC q7d	
Xylazine	Rompun	1.1 mg/kg IV; 2.2 mg/kg SC, IM	(cats) 0.4-0.5 mg/kg IM or IV for emesis	

## PART FOUR

# HEPATOBILIARY AND EXOCRINE PANCREATIC DISORDERS

Penny J. Watson and Susan E. Bunch

CHAPTER

## Clinical Manifestations of Hepatobiliary Disease



#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS ABDOMINAL ENLARGEMENT

Organomegaly
Abdominal Effusion
Abdominal Muscular Hypotonia
JAUNDICE, BILIRUBINURIA, AND CHANGE IN FECAL
COLOR
HEPATIC ENCEPHALOPATHY
COAGULOPATHIES
POLYURIA AND POLYDIPSIA

#### **GENERAL CONSIDERATIONS**

Clinical signs of hepatobiliary disease in cats and dogs can be extremely variable, ranging from anorexia and weight loss to abdominal effusion, jaundice, and hepatic coma (Box 35-1). However, none of these signs are pathognomonic for hepatobiliary disease, and they must be distinguished from identical signs caused by disease of other organ systems. The severity of the clinical sign does not necessarily correlate with the prognosis or with the degree of liver injury, although several of these signs are often seen together in dogs and cats with end-stage hepatic disease (e.g., ascites, metabolic encephalopathy from hepatocellular dysfunction, and acquired portosystemic venous shunting with gastrointestinal bleeding); however, ascites has recently been shown to be a significant negative prognostic indicator in dogs with chronic hepatitis. At the opposite end of the spectrum of hepatobiliary disease, because of the tremendous reserve capacity of the liver, there may be no clues for the presence of a hepatic disorder except for abnormal screening blood test results obtained before an elective anesthetic procedure.

#### ABDOMINAL ENLARGEMENT

#### **ORGANOMEGALY**

Abdominal enlargement may be the presenting complaint of owners of cats and dogs with hepatobiliary disease, or it may be noted during physical examination. Organomegaly, fluid expansion of the peritoneal space, or poor abdominal muscle tone is usually the cause of this abnormality.

Enlarged organs that most often account for increased abdominal size are the liver, the spleen (see Chapter 88), and occasionally the kidneys (see Chapter 41). Normally, the liver is palpable just caudal to the costal arch along the ventral body wall in the cat and dog, but it may not be palpable at all. Inability to palpate the liver, especially in dogs, does not automatically mean that the liver is abnormally small. In lean cats it is usually possible to palpate the diaphragmatic surface of the liver. In cats or dogs with pleural effusion or other diseases that expand thoracic volume, the liver may be displaced caudally and erroneously appear to be enlarged.

Liver enlargement is much more common in cats than in dogs with liver disease. Dogs more often have reduced liver size because of chronic hepatitis with fibrosis. The pattern of liver enlargement may be generalized or focal, depending on the cause. Infiltrative and congestive disease processes or those that stimulate hepatocellular hypertrophy or mononuclear-phagocytic system (MPS) hyperplasia tend to result in smooth or slightly irregular, firm, diffuse hepatomegaly. Focal or asymmetrical hepatic enlargement is often seen with proliferative or expansive diseases that form solid or cystic mass lesions. Examples of such diseases are listed in Table 35-1.

Smooth, generalized hepatosplenomegaly may be associated with nonhepatic causes, such as increased intravascular hydrostatic pressure (passive congestion) secondary to right-sided congestive heart failure or pericardial disease. In rare instances hepatic vein occlusion (Budd-Chiari syndrome)



BOX 35-1

Clinical Signs and Physical Examination Findings in Cats and Dogs with Hepatobiliary Disease

General, Nonspecific
Anorexia
Depression
Lethargy
Weight loss
Small body stature
Poor or unkempt haircoat
Nausea, vomiting
Diarrhea
Dehydration
Polydipsia, polyuria
More Specific But Not Pathognomonic
Abdominal enlargement (organomegaly, effusion, or mus- cular hypotonia) Jaundice, bilirubinuria, acholic feces Metabolic encephalopathy Coagulopathies

results in similar findings. Hepatosplenomegaly in icteric dogs or cats may be attributable to benign MPS hyperplasia and extramedullary hematopoiesis secondary to immunemediated hemolytic anemia or to infiltrative processes such as lymphoma, systemic mast cell disease, or myeloid leukemia.

Another cause of hepatosplenomegaly is primary hepatic parenchymal disease with sustained intrahepatic portal hypertension. In dogs and cats with this syndrome, the liver is usually firm and irregular on palpation and often the liver itself is reduced in size as a result of fibrosis; however, the spleen can be enlarged and congested as a result of portal hypertension. For conditions that involve primarily the spleen, see Chapter 88.

#### ABDOMINAL EFFUSION

Abdominal effusion is much more common in dogs than in cats with liver disease. With the exception of liver disease associated with feline infectious peritonitis (FIP), cats with liver disease rarely have ascites. The pathogenesis of abdominal effusion in cats and dogs with hepatobiliary disease is determined by chemical and cytologic analysis of a fluid specimen (Fig. 35-1; see also Table 36.1). On the basis of cell and protein content, abdominal fluids are classified by standard criteria as transudates, modified transudates (moderate to low cellularity with moderate to low protein concentration), or chyle or blood (see Table 36-1). The term *ascites* is reserved for fluid of low to moderate protein content and low to moderate cell count (transudate or modified transudate) and is usually related to disorders of hepatic or cardiovascu-



Differential Diagnoses for Changes in Hepatic Size

DIAGNOSIS	SPECIES
Hepatomegaly Generalized	
Infiltration	
Primary or metastatic neoplasia	C, D
Cholangitis	С
Extramedullary hematopoiesis*	C, D
Mononuclear-phagocytic cell	C, D
hyperplasia*	
Amyloidosis (rare)	C, D
Passive congestion*	
Right-sided heart failure	C, D
Pericardial disease	D
Caudal vena cava obstruction	D
Caval syndrome	D
Budd-Chiari syndrome (rare)	C, D
Lipidosis	C (moderate
	to marked),
Hypercorticolism (storoid hongtonathy)	D (mild) D
Hypercortisolism (steroid hepatopathy) Anticonvulsant drug therapy	D
Acute extrahepatic bile duct obstruction	C, D
Acute hepatotoxicity	C, D
Focal or asymmetric	0, 5
	<i>a</i>
Primary or metastatic neoplasia	C, D
Nodular hyperplasia	D
Chronic hepatic disease with fibrosis and	D
nodular regeneration	C D
Abscess(es) (rare)	C, D C, D
Cysts (rare)	C, D
Microhepatia (Generalized Only)	
Reduced hepatic mass†	
Chronic hepatic disease with	D
progressive loss of hepatocytes	
Decreased portal blood flow with	
hepatocellular atrophy	
Congenital portosystemic shunt	C, D
Intrahepatic portal vein hypoplasia	D
Chronic portal vein thrombosis	D
Hypovolemia	0
Shock?	ŝ
Addison's disease	D

<sup>\*</sup> Concurrent splenomegaly likely.

lar origin or severe protein-losing enteropathy or nephropathy. A small amount of effusion is suspected when abdominal palpation yields a "slippery" sensation during physical examination. Moderate-to-large-volume effusion is frequently conspicuous but may distend the abdomen so

<sup>†</sup>Loss of portal blood flow to one lobe can cause the lobe to atrophy. *C,* Primarily cats; *D,* primarily dogs; *C, D,* cats and dogs.

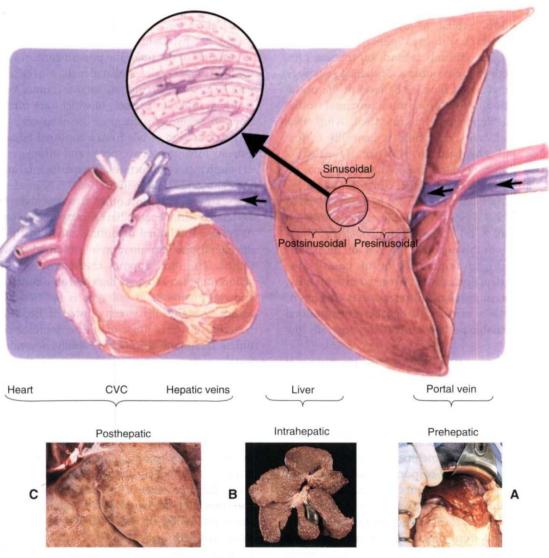


FIG 35-1

Mechanisms of abdominal fluid accumulation associated with altered portal and hepatic blood flow and clinical correlates. PREHEPATIC: arteriovenous fistula (A) or portal vein obstruction or hypoplasia; INTRAHEPATIC presinusoidal: periportal fibrosis or portal venule hypoplasia; INTRAHEPATIC sinusoidal: cellular infiltrates or collagen (B); INTRAHEPATIC postsinusoidal: central (terminal hepatic) venular fibrosis; POSTHEPATIC (passive congestion): obstruction of hepatic veins or intrathoracic caudal vena cava, right-sided heart failure (C) or pericardial disease. Arrow indicates direction of venous blood flow. (From Johnson SE: Portal hypertension. I. Pathophysiology and clinical consequences, Compend Contin Educ 9:741, 1987.)

much that details of abdominal organs are obscured during palpation. Whether there is small- or large-volume effusion, the general pathogeneses of third-space fluid accumulation (excessive formation by increased venous hydrostatic pressure, decreased intravascular oncotic pressure, or altered vascular permeability and insufficient resorption), singly or in combination, apply to cats and dogs with hepatobiliary diseases. In addition, an important part of the mechanisms of ascites formation in dogs with liver disease is activation of the renin-angiotensin-aldosterone system (RAAS) with

sodium retention by the kidneys and increased circulating fluid volume. This RAAS activation is triggered by a decrease in systemic blood pressure caused by pooling of a significant proportion of the circulating blood volume in the splanchnic circulation. It has been observed that, in many cases, overt ascites does not develop until sodium retention by the kidneys is increased, altering the balance of fluid formation and reabsorption. Therefore aldosterone antagonists play a key role in the treatment of ascites associated with liver disease.

Intrahepatic portal venous hypertension is the most common mechanism leading to ascites in companion animals, particularly dogs, with hepatobiliary diseases. The formation of abdominal effusion depends on the site, rate, and degree of defective venous outflow. Sustained resistance to intrahepatic portal blood flow at the level of the portal triad favors exudation of fluid from more proximal (in the direction of portal blood flow; i.e., intestinal) lymphatics into the abdominal cavity. The fluid is generally of low protein content and is hypocellular. However, if the fluid is present in the abdomen for any amount of time, it becomes "modified" with an increase in protein content. The exception to this is in the animal with marked hypoalbuminemia associated with liver disease in which the ascites remains a low-protein transudate. Inflammatory or neoplastic cellular infiltrates or fibrosis in this region of the liver are the pathologic processes most often responsible for this type of effusion. Sinusoidal obstruction caused by regenerative nodules, collagen deposition, or cellular infiltrates causes effusion of a fluid composed of a mixture of hepatic and intestinal lymph that has a variable protein content and generally low cell count.

Prehepatic portal venous occlusion or the presence of a large arteriovenous fistula, leading to portal venous volume overload, and associated high intrahepatic vascular resistance triggered by increased portal flow also produces a low to moderate protein, hypocellular effusion, as would diffuse mesenteric lymphatic obstruction associated with lymphoma. The latter can also sometimes result in a chylous effusions. Examples of causes of portal venous occlusion include intrahuminal obstructive masses (e.g., thrombus), extrahuminal compressive masses (e.g., mesenteric lymph node, neoplasm), and portal vein hypoplasia or atresia.

Venous congestion from disease of the major hepatic veins and/or distally (i.e., thoracic caudal vena cava, heart; posthepatic venous congestion) increases formation of hepatic lymph, which exudes from superficial hepatic lymphatics. Because the endothelial cell-lined sinusoids are highly permeable, hepatic lymph is of high protein content. Abdominal effusion formed under these conditions is more likely to develop in dogs than in cats. Reactive hepatic veins that behave as postsinusoidal sphincters have been identified in dogs and are speculated to add to venous outflow impingement. Concurrent hypoalbuminemia (≤1.5 g/dl) in dogs (and rarely cats) associated with hepatic parenchymal failure may further enhance movement of fluid into the peritoneal space. Perivenular pyogranulomatous infiltrates in the visceral and parietal peritoneum of cats with the effusive form of FIP increase vascular permeability and promote exudation of straw-colored, protein-rich fluid into the peritoneal space. Typically, the fluid is of low to moderate cellularity, with a mixed cell population of neutrophils and macrophages, and with a moderate to high protein concentration. It is usually classified as an exudate but occasionally is a modified transudate.

Hepatobiliary malignancies or other intraabdominal carcinomas that have disseminated to the peritoneum can elicit an inflammatory reaction, with subsequent exudation of lymph and fibrin. The fluid may be serosanguineous, hemorrhagic, or chylous in appearance. Regardless of the gross appearance of the fluid, the protein content is variable, and the fluid may contain exfoliated malignant cells if the primary neoplasm is a carcinoma, mesothelioma, or lymphoma, although often it does not, in which case further investigations are required to diagnose the neoplasm.

Extravasation of bile from a ruptured biliary tract elicits a strong inflammatory response and stimulates transudation of lymph by serosal surfaces. In experimental animal models, the damaging component of bile has been identified as bile acids. Unlike with most other causes of abdominal effusion associated with hepatobiliary disease, there may be evidence of cranial abdominal or diffuse abdominal pain identified during physical examination in cats and dogs with bile peritonitis. The fluid appears characteristically dark orange, yellow, or green and has a high bilirubin content on analysis, and the predominant cell type is the healthy neutrophil, except when the biliary tract is infected. Because normal bile is sterile, the initial phase of bile peritonitis is nonseptic, but unless treatment is initiated rapidly, secondary infection, usually with anaerobes, may become life-threatening.

#### **ABDOMINAL MUSCULAR HYPOTONIA**

The presence of a distended abdomen in the absence of organomegaly or abdominal effusion suggests abdominal muscular hypotonia. Either the catabolic effects of severe malnutrition or (more commonly in dogs) excess endogenous or exogenous corticosteroids reduce muscular strength, giving the appearance of an enlarged abdomen. In both dogs and (much less commonly) cats with hyperadrenocorticism, the combination of generalized hepatomegaly (mild and associated with diabetes mellitus in cats), redistribution of fat stores to the abdomen, and muscular weakness causes abdominal distention.

On the basis of the physical examination findings, the problem of abdominal enlargement should be refined to the level of organomegaly, abdominal effusion, or poor muscular tone, as shown in Fig. 35-2. Additional tests are required to obtain a definitive diagnosis.

## JAUNDICE, BILIRUBINURIA, AND CHANGE IN FECAL COLOR

By definition, jaundice in cats and dogs is the yellow staining of serum or tissues by an excessive amount of bile pigment or bilirubin (Fig. 35-3); the terms *jaundice* and *icterus* may be used interchangeably. Because the normal liver has the ability to take up and excrete a large amount of bilirubin, there must be either a large, persistent increase in the production of bile pigment (hyperbilirubinemia) or a major impairment in bile excretion (cholestasis with hyperbilirubinemia) before jaundice is detectable as yellow-stained tissues (serum bilirubin concentration ≥2 mg/dl) or serum (serum bilirubin concentration ≥1.5 mg/dl).

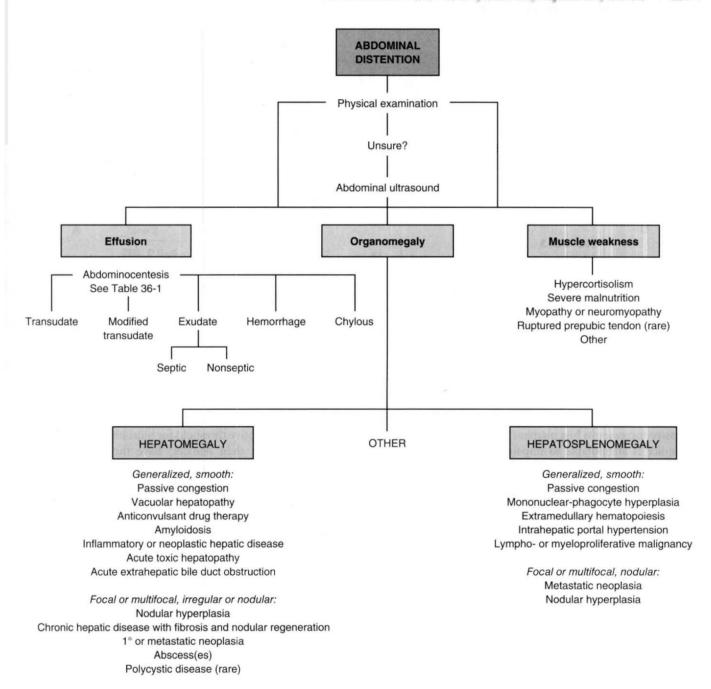


FIG 35-2

Algorithm for initial evaluation of the cat or dog with abdominal distention.

In normal animals bilirubin is a waste product of heme protein degradation. The primary source of heme proteins is senescent erythrocytes, with a small contribution by myoglobin and heme-containing enzyme systems in the liver. After phagocytosis by cells of the MPS, primarily in the bone marrow and spleen, heme oxygenase opens the protoporphyrin ring of hemoglobin, forming biliverdin. Biliverdin reductase converts biliverdin to fat-soluble bilirubin IXa, which is released into the circulation, where it is bound to albumin for transport to hepatic sinusoidal membranes. After uptake, transhepatocellular movement, and conjuga-

tion to various carbohydrates, conjugated bilirubin, now water soluble, is excreted into the bile canaliculi. Conjugated bilirubin is then incorporated into micelles and stored with other bile constituents in the gallbladder until it is discharged into the duodenum. However, in dogs it has been noted that only 29% to 53% of bile produced is stored in the gall bladder; the rest is secreted directly into the duodenum (Rothuizen et al., 1990). After arrival in the intestine, conjugated bilirubin undergoes bacterial deconjugation and then reduction to urobilinogen, with most urobilinogen being resorbed into the enterohepatic circulation. A small fraction



FIG 35-3

Jaundiced mucous membranes in a dog (A, gum, and B, sclera). Note that this dog had jaundice because of immune-mediated hemolytic anemia and not liver disease—hence the mucous membranes are pale and yellow (which makes them more easily photographed). (Photographs courtesy Sara Gould.)

of urobilinogen is then excreted in the urine, and a small portion remains in the intestinal tract to be converted to stercobilin, which imparts normal fecal color.

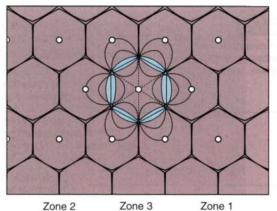
Inherited abnormalities of bilirubin metabolism have not been identified in cats and dogs; thus in the absence of massive increases in bile pigment production by hemolysis, jaundice is attributable to impaired excretion of bilirubin (and usually other constituents of bile) by diffuse intrahepatic hepatocellular or biliary disease or by interrupted delivery of bile to the duodenum. The inability to take up, intracellularly process, or excrete bilirubin into the bile canaliculi (the rate-limiting step) is the mechanism of cholestasis believed to be operational in many primary hepatocellular diseases. Jaundice is more likely to be a clinical feature if the liver disorder involves primarily the periportal (zone 1) hepatocytes (Fig. 35-4) than if the lesion involves centrilobular (zone 3) hepatocytes. Inflammation and swelling of larger intrahepatic biliary structures could similarly delay bile excretion.

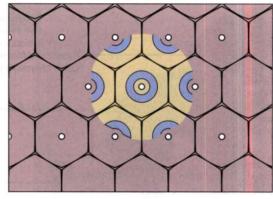
Obstruction of the bile duct near the duodenum results in increased intraluminal biliary tract pressure, interhepatocellular regurgitation of bile constituents into the circulation, and jaundice. If only one of the hepatic bile ducts exiting the liver is blocked or if only the cystic duct exiting the gallbladder is obstructed for some reason, there may be biochemical clues for localized cholestasis, such as high serum alkaline phosphatase activity; however, the liver's overall ability to excrete is preserved, and jaundice does not ensue. Traumatic or pathologic biliary tract rupture allows leakage of bile into the peritoneal space and some absorption of bile components. Depending on the underlying cause and the time elapsed between biliary rupture and diagnosis, the degree of jaundice may be mild to moderate. If biliary rupture has occurred, the total bilirubin content of the abdominal effusion is greater than that of serum.

Reference ranges for serum total bilirubin concentrations in dogs and cats may vary from laboratory to laboratory, but most published resources agree that concentrations over 0.3 mg/dl in cats and 0.6 mg/dl in dogs are abnormal. When results of laboratory tests are assessed, species differences in the formation and renal processing of bilirubin between cats and dogs must be taken into account. Canine renal tubules have a low resorptive threshold for bilirubin. Dogs (males to a greater extent than females) have the necessary renal enzyme systems to process bilirubin to a limited extent; therefore bilirubinuria (up to 2+ to 3+ reaction by dipstick analysis) may be a normal finding in canine urine specimens of specific gravity greater than 1.025. Cats do not have this ability, and they have a ninefold higher tubular absorptive capacity for bilirubin than dogs. Bilirubinuria in cats is associated with hyperbilirubinemia and is always pathologic. Because unconjugated and most conjugated bilirubin is albumin-bound in the circulation, only the small amount of nonprotein-bound conjugated bilirubin is expected to appear in the urine in physiologic and pathologic states. In dogs with hepatobiliary disease, increasing bilirubinuria often precedes the development of hyperbilirubinemia and clinical jaundice and may be the first sign of illness detected by owners.

Several nonhepatobiliary disorders impede bilirubin excretion by poorly understood means. Jaundice with evidence of hepatocellular dysfunction but minimal histopathologic changes in the liver has been described in septic human, feline, and canine patients. Certain products released by bacteria, such as endotoxin, are known to reversibly interfere with bile flow. As yet unexplained mild hyperbilirubinemia (2.5 mg/dl) may also be detected in approximately 20% of hyperthyroid cats. Experimental investigations of thyrotoxicosis in laboratory animals have demonstrated increased production of bilirubin, which has been proposed to be associated with increased degradation of hepatic heme proteins. There is no histologic evidence of cholestasis at the light microscopic level in affected cats, and the hyperbilirubinemia resolves with return to euthyroidism. Guidelines for

В





#### FIG 35-4

**A,** Rappaport scheme of the hepatic functional lobule (acinus), organized according to biochemical considerations (1958). For example, zone 1 cells are responsible for protein synthesis, urea and cholesterol production, gluconeogenesis, bile formation, and cytogenesis; zone 2 cells also produce albumin and are actively involved in glycolysis and pigment formation; and zone 3 cells are the major site of liponeogenesis, ketogenesis, and drug metabolism. Zone 3 hepatocytes, being farther from the hepatic artery and hepatic portal veins, also have the lowest oxygen supply and are therefore most susceptible to hypoxic damage. Conversely, zone 1 hepatocytes, being closest to the hepatic portal vein, are most susceptible to damage by toxins from the gut. **B,** Outdated theory of hepatic functional lobule, as first proposed in 1833. The apparent hexagonal boundaries have little to do with functional arrangement.

initial evaluation of the icteric cat or dog are given in Fig. 35-5. Finally, lipemia is a common cause of pseudohyper-bilirubinemia in dogs as a result of interference with the laboratory test.

Acholic feces result from total absence of bile pigment in the intestine (Fig. 35-6). Only a small amount of bile pigment is needed to be changed to stercobilin and yield normal fecal color; therefore bile flow into the intestine must be completely discontinued in order to form acholic feces, and this is very rare in both dogs and cats. In addition to appearing pale from lack of stercobilin and other pigments, acholic feces are pale because of steatorrhea resulting from the lack of bile acids to facilitate fat absorption. Mechanical diseases of the extrahepatic biliary tract (e.g., unremitting complete extrahepatic bile duct obstruction [EBDO], traumatic bile duct avulsion from the duodenum) are the most common causes of acholic feces in cats and dogs. Total inability to take up, conjugate, and excrete bilirubin because of generalized hepatocellular failure is theoretically possible. However, because the functional organization of the liver is heterogeneous (see Fig. 35-4) and because primary hepatic diseases do not affect all hepatocytes uniformly, the overall ability of the liver to process bilirubin may be altered, although it is usually preserved. A condition has been reported rarely in cats with severe cholangitis in which bile flow ceases. Under these circumstances, "bile" consists of only clear, viscous biliary epithelial secretions, and this may result in the production of acholic feces. A similar finding, known as "white bile syndrome," has been associated with prolonged total biliary obstruction and is thought to be the result of resorption of bile pigments. The true frequency of white bile in cats or dogs with severe cholestasis is not known.

#### HEPATIC ENCEPHALOPATHY

Signs of abnormal mentation and neurologic dysfunction develop in dogs and cats with serious hepatobiliary disease as a result of exposure of the cerebral cortex to absorbed intestinal toxins that have not been removed by the liver. Substances that have been implicated as important in the genesis of hepatic encephalopathy (HE), singly or in combination, are ammonia, mercaptans, short-chain fatty acids, skatoles, indoles, and aromatic amino acids. Either there is marked reduction in functional hepatic mass or portal blood flow has been diverted by the development of portosystemic venous anastomoses, thus preventing detoxification of gastrointestinal (GI) toxins, or there is a combination of these two processes. Portosystemic shunting can occur via the presence of a macroscopic vascular pattern that results from a congenital vascular miscommunication or by a complex of acquired "relief valves" that open in response to sustained portal hypertension secondary to severe primary hepatobiliary disease (Fig. 35-7). Intrahepatic, microscopic portosystemic shunting or widespread hepatocellular inability to detoxify noxious enteric substances accounts for HE when an abnormal portal vascular pattern cannot be demonstrated. Rarely, if congenital portovascular anomalies and severe primary hepatobiliary disease with acquired shunting have been ruled out, congenital urea enzyme cycle deficiencies

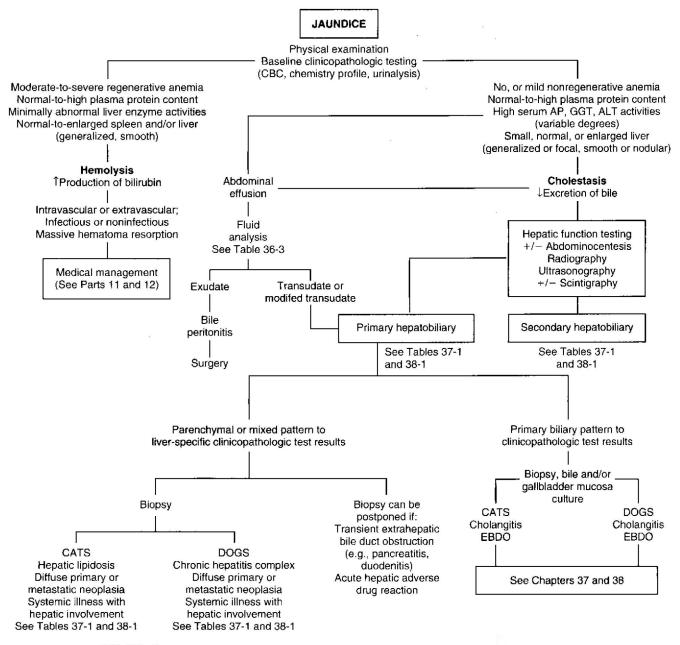


FIG 35-5
Algorithm for preliminary evaluation of the icteric cat or dog. AP, Alkaline phosphatase; GGT, γ-glutamyltransferase; ALT, alanine transaminase; EBDO, extrahepatic bile duct obstruction.

and organic acidemias, in which ammonia cannot be degraded to urea, are considered. HE has also been reported in congenital cobalamin deficiency in dogs (Battersby et al., 2005). Animals with systemic diseases having hepatic manifestations do not undergo sufficient loss of hepatic mass or change in hepatic blood flow to develop signs of HE.

The pathogenesis of this reversible abnormality in cerebral metabolism currently is incompletely understood. Increased ammonia (NH<sub>3</sub>) in the blood remains the most important cause of HE. Most of the precipitating factors and treatment recommendations for HE primarily affect blood NH3 concentrations. The effects on neurotransmitters and

the cerebrospinal fluid (CSF) environment are complex. The brain is very sensitive to the toxic effects of NH<sub>3</sub> but does not have a urea cycle, so NH<sub>3</sub> in the CSF is detoxified to glutamine. CSF glutamine concentrations in dogs with portosystemic shunts (PSS) correlate better with clinical signs than CSF or blood NH<sub>3</sub> levels (Fig. 35-8). Dogs with congenital PSS also have increased CSF concentrations of aromatic amino acids, particularly tryptophan and its metabolites, and this appears to be directly related to NH<sub>3</sub> concentrations in the CSF because they share an antiport transporter. Also implicated are changes in central nervous system (CNS) serotonin activity (which is often reduced);



FIG 35-6
Acholic feces from a 7-year-old spayed female Collie dog with a strictured bile duct and complete bile duct obstruction 3 weeks after recovery from severe pancreatitis.

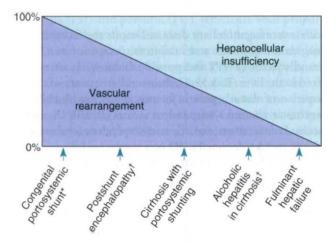


FIG 35-7
Spectrum of hepatic encephalopathy in cats and dogs ranging from pure vascular to pure hepatocellular causes.
\*, Clinically relevant only in dogs and cats; †, clinically relevant only in human patients. (Modified from Schafer DF et al: Hepatic encephalopathy. In Zakim D et al, editors: Hepatology: a textbook of liver disease, Philadelphia,

1990, WB Saunders.)

stimulation of NMDA (*N*-methyl-D-aspartic acid) receptors, peripheral-type benzodiazepine receptors, and altered astrocyte receptors and handling of glutamate. Most of these changes are related to increased NH<sub>3</sub>.

The sources of increased blood ammonia in animals with liver disease are outlined in Fig. 35-9 and include the following:

- Bacterial breakdown of undigested amino acids and purines that reach the colon
- Bacterial and intestinal urease action on urea, which freely diffuses into the colon from the blood
- Small intestinal enterocyte catabolism of glutamine as their main energy source





FIG 35-8

Two dogs with similar fasting plasma ammonia concentrations, emphasizing the lack of correlation between plasma ammonia content and severity of encephalopathic signs. **A,** Female Miniature Poodle with congenital portosystemic shunt. The plasma ammonia concentration was 454 µg/dl. **B,** Male mixed-breed dog with chronic hepatic failure and acquired portosystemic shunting. The plasma ammonia concentration was 390 µg/dl.

 Endogenous hepatic protein metabolism from excess dietary protein, GI bleeding, or breakdown of lean body mass

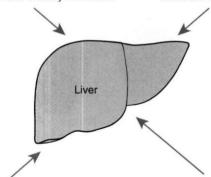
It is very important to realize that the traditional view that the toxins causing HE are predominantly of dietary origin is misleading; although the gut is an important source of NH<sub>3</sub> in animals on high-protein diets, in many animals, particularly those with protein-calorie malnutrition, endogenous sources of NH<sub>3</sub> may be more important and further dietary protein restriction just worsens the hyperammonemia in these cases.

Subtle, nonspecific signs of HE in cats and dogs that could be noted at any time and that represent chronic or subclinical HE include anorexia, depression, weight loss, lethargy, nausea, fever, hypersalivation (particularly in cats), intermittent vomiting, and diarrhea. Certain events might precipitate an acute episode of HE with severe neurologic signs (see Chapter 39). Nearly any CNS sign may be observed in cats and dogs with HE, although typical signs tend to be nonlo-

#### Ammonia derived from other organs:

Metabolism of body protein when in negative nitrogen balance Accentuated by inflammatory disease and likely by cytokines/inflammatory mediators

Hepatic transamination and deamination of amino acids for energy or to make other amino acids when excess or poor quality amino acids are fed



#### Gut derived ammonia: Metabolism of glutamine

by small intestinal enterocytes as their main energy source (obligate)

Bacterial degradation of undigested protein in the colon (should be minimal on a digestible protein diet)

#### FIG 35-9

Sources of ammonia that can contribute to hepatic encephalopathy: Note that it is now believed that bacterial degradation of undigested protein in the colon is the least important of these on normal diets.



BOX 35-2

Typical Clinical Signs of Hepatic Encephalopathy in Dogs and Cats

Lethargy Depression Behavioral changes Head pressing Circling Pacing Central blindness Seizures (uncommon)

Coma (uncommon) Hypersalivation (especially cats)

calizing, suggesting generalized brain involvement: trembling, ataxia, hysteria, dementia, marked personality change (usually toward aggressiveness), circling, head pressing, cortical blindness, or seizures (see Box 35-2). Ocassionally, animals with hyperammonemia have asymmetric, localizing neurologic signs that regress with appropriate treatment for HE.

#### **COAGULOPATHIES**

Because of the integral role of the liver in hemostasis, hemorrhagic tendencies can be a presenting sign in cats and dogs



BOX 35-3

#### Coagulation Proteins and Inhibitors Synthesized by the Liver

```
Proteins C and S
Antithrombin
Fibrinogen
Plasminogen
Vitamin K-dependent factors
   II (prothrombin)
  IX
  X
Factor V
Factor XI
Factor XII
Factor XIII
```

with severe hepatobiliary disease. Despite the fact that most coagulation proteins and inhibitors, except for von Willebrand's factor (vWF) and possibly factor VIII, are synthesized in the liver (Box 35-3), the overall frequency of clinical sequelae of disturbances in hemostasis is low. Inability to synthesize vitamin K-dependent factors (II, VII, IX, and X) because of the absence of bile acid-dependent fat absorption secondary to complete EBDO or a transected bile duct from abdominal trauma can cause clinically apparent bleeding. Subclinical and clinical coagulopathies are also noted in animals with severe diseases of the hepatic parenchyma. Some animals with severe hepatic disease and relatively unremarkable results of routine coagulation tests have high serum activity of proteins induced by vitamin K antagonism (PIVKA) that could impart bleeding tendencies. In early studies of the mechanism of impaired coagulation after partial hepatectomy in dogs, after surgical removal of 70% of the hepatic mass, dogs developed significant alterations in plasma clotting factor concentrations without spontaneous hemorrhage. Having severe hepatic parenchymal disease predisposes a dog or cat not only to changes in coagulation factor activity from hepatocellular dysfunction but also to disseminated intravascular coagulation (DIC), particularly in those with acute disease (see Chapter 38). In dogs with acute hepatic necrosis, some clinicians have observed thrombocytopenia, thought to be associated with increased platelet use or sequestration.

Other than noticeable imbalances in coagulation factor activity, the only other mechanism by which bleeding might occur in a cat or dog with severe hepatic disease is portal hypertension-induced vascular congestion and fragility. In such cases, which are expected considerably more often in dogs than in cats because of the types of hepatobiliary diseases they acquire, the common site affected is the upper GI tract (stomach, duodenum); therefore hematemesis and melena are common bleeding presentations and a common cause of death in dogs with chronic liver disease. In contrast

to human patients, in whom fragile esophageal varices develop and can burst, causing severe and often fatal hemorrhage, the mechanism of GI hemorrhage in companion animals is unknown but is suspected to be related to poor mucosal perfusion and reduced epithelial cell turnover associated with portal hypertension and splanchnic pooling of blood. Hypergastrinemia was observed in dogs made cirrhotic under experimental conditions and was theorized to have been provoked by excess serum bile acid concentrations. More recent studies have not borne out this theory; in fact, gastrin is often low in dogs with liver disease, and the ulcers are often duodenal and not gastric.

#### POLYURIA AND POLYDIPSIA

Increased thirst and volume of urination can be clinical signs of serious hepatocellular dysfunction and also of portosystemic shunts. Several factors are suspected to contribute to polydipsia (PD) and polyuria (PU), which are seen primarily in dogs and rarely in cats, with marked hepatic dysfunction. Altered sense of thirst may be a manifestation of HE. Dogs with congenital and acquired PSS have hypercortisolemia associated with reduced metabolism of cortisol in the liver and decreased cortisol binding protein concentration in the plasma. Excess secretion of adrenocorticotropic hormone stimulated by abnormal neurotransmitters leads to excess cortisol secretion and altered threshold for antidiuretic hormone release in dogs with HE. Secondary hyperaldosteronism from delayed excretion of aldosterone, which is accomplished normally by the liver, leads to sodium reten-

tion and increased water intake with compensatory PU. Changes in the function of portal vein osmoreceptors that stimulate thirst without hyperosmolality are also thought to be partly responsible for PD. Loss of the renal medullary concentrating gradient for urea because of the inability to produce urea from ammonia would first cause PU and then compensatory PD. Delayed cortisol excretion and persistent hypokalemia may also contribute to the renal concentrating defect. Investigation of polydipsia in dogs with congenital PSS has identified partial renal concentrating ability in response to water deprivation, with resolution of PD when normal portal blood flow was reestablished.

#### Suggested Readings

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# C H A P T E R Diagnostic Tests for the Hepatobiliary System

#### CHAPTER OUTLINE

DIAGNOSTIC APPROACH DIAGNOSTIC TESTS

Tests to Assess Status of the Hepatobiliary System
Tests to Assess Function of the Hepatobiliary System
Urinalysis
Fecal Evaluation
Abdominocentesis/Fluid Analysis
Complete Blood Count
Coagulation Tests
DIAGNOSTIC IMAGING
Survey Radiography
Ultrasonography

Ultrasonography
Scintigraphy
LIVER BIOPSY

#### DIAGNOSTIC APPROACH

Because the liver is physiologically and anatomically diverse, no single test adequately identifies liver disease or its underlying cause. For this reason, a battery of tests must be used to assess the hepatobiliary system. Many of these tests just show liver involvement in a disease process and do not evaluate liver function. A reasonable package of screening tests recommended for an animal suspected of having hepatobiliary disease includes a complete blood count (CBC), serum biochemical profile, urinalysis, fecal analysis, and survey abdominal radiographs or ultrasonography. Results of these tests may suggest evidence of hepatobiliary disease that can be confirmed by other, more specific tests. It is important at this stage to rule out secondary hepatopathy and rule in primary liver disease because with hepatopathies secondary to other diseases, time and resources should be devoted as soon as possible to identifying and treating the underlying cause rather than investigating the liver. The need for other laboratory tests (e.g., serum bile acid [SBA], abdominocentesis, coagulation profile) is determined by each animal's history and physical examination findings.

Of the recommended screening tests for hepatobiliary disease, the serum biochemistry profile offers specific information regarding the distribution and activity or status (e.g., hyperbilirubinemia, enzyme activities) of a hepatobiliarydisorder and an estimate of the degree of functional impairment (e.g., inadequate protein synthesis, altered toxin excretion). Determining hepatic functional capacity adds a meaningful dimension to the diagnostic evaluation and permits construction of a reasonable list of differential diagnoses and tentative assignment of prognosis. It is important to remember that some hepatobiliary diseases are characterized by subtle changes in enzyme activity in association with severe functional disturbance, and some have high enzyme activities and normal functional indices. Because of the large reserve capacity of the liver, detection of global hepatic functional impairment by conventional means is not possible until there is at least 55% loss of hepatic mass. Diseases that cause acute hepatocyte loss show evidence of functional impairment more quickly than diseases with chronic hepatocyte loss, wherein the remaining hepatocytes have time to compensate. In dogs with chronic hepatitis, signs of functional impairment may not be evident until 75% of hepatic mass has been lost. The recommended serum biochemistry profile for liver disease includes, in addition to liver enzymes, albumin, urea nitrogen, bilirubin, cholesterol, and glucose concentrations, which are used to assess the ability of the liver to synthesize proteins, detoxify protein degradation products, excrete organic anions and other substances, and help maintain euglycemia, respectively. Development of automated methods for laboratory analysis has made measurement of many substances in the blood easy; these laboratory analytic methods are available at competitive prices through commercial laboratories or as point-of-care test kits or systems. For this reason, there is no excuse for excluding a multiple component serum biochemistry profile from the initial diagnostic plan for a cat or dog suspected of having hepatobiliary disease.

A sensitive, although relatively nonspecific, test of hepatobiliary function is determination of fasting and postprandial SBA concentrations. Serum bile acid concentrations are measured if there are persistent liver-specific serum biochemical abnormalities or a liver problem is suspected (e.g., microhepatia, ammonium biurate crystalluria) but results of routine diagnostic tests are inconclusive. Serum bile acids are not a helpful test of liver function in a jaundiced animal because they are also elevated in cholestasis because of decreased excretion, independent of liver function. Bile acids are not available on usual practice analyzers, but a point-of-care snap test for SBA estimation has recently become available in the United States (IDEXX Laboratories, Westbrook, ME).

Results of laboratory evaluation reflect one point in time in a spectrum of dynamic changes. If the test results are equivocal and the clinical signs are vague, sequential evaluation may be necessary to allow time for the disease to be fully expressed.

By using a combination of history, physical examination findings, and results of screening and hepatobiliary-specific laboratory tests, the clinician should be able to describe the disorder as primary or secondary (reactive) hepatopathy, active or quiescent; characterize the pattern of hepatobiliary disease as primarily hepatocellular, primarily biliary, or mixed hepatobiliary; and estimate the degree of hepatobiliary dysfunction. From this same information, an animal may be described clinically as having hepatic disease, with evidence of hepatic abnormalities such as high liver enzyme activities and hepatomegaly, or hepatic failure, in which there is a state of multiple function loss. Some primary hepatic diseases may progress to failure; most secondary hepatic diseases do not (Tables 37-1 and 38-1). Use of the term failure often inappropriately connotes a poor prognosis. If the underlying cause can be removed full recovery is possible. Most important, before an accurate prognosis can be given, a complete evaluation must be conducted, including, for most primary hepatobiliary diseases in both dogs and cats, a liver biopsy.

#### **DIAGNOSTIC TESTS**

# TESTS TO ASSESS STATUS OF THE HEPATOBILIARY SYSTEM Serum Enzyme Activities

Liver-specific serum enzyme activities are included routinely in screening serum biochemistry panels and are regarded as markers of hepatocellular and biliary injury and reactivity. Because marked hepatic disease can be present in patients with normal serum enzyme activity, finding normal values should not preclude further investigation, especially if there are clinical signs or other laboratory test results that suggest hepatobiliary disease. Increased serum activity of enzymes normally located in hepatocyte cytosol in high concentration reflects structural or functional cell membrane injury that would allow these enzymes to escape or leak into the blood. The two enzymes found to be of most diagnostic use in cats and dogs are alanine transaminase (ALT; glutamic-pyruvic transaminase [GPT]) and aspartate transaminase (AST; glutamic-oxaloacetic transaminase [GOT]). Because ALT is found principally in hepatocytes and AST (also located

within hepatocyte mitochondria) has a wider tissue distribution (e.g., in muscle), ALT is the enzyme selected to most accurately reflect hepatocellular injury. Less is known about the behavior of AST in various hepatobiliary diseases in companion animals, although some studies have indicated that AST is a more reliable indicator of liver injury in cats. Several studies have demonstrated mild to moderately high serum ALT activity (without histologic or biochemical evidence of liver injury), in addition to expected high serum activities of muscle-specific creatine kinase and AST, in dogs with skeletal muscle necrosis.

In general, the magnitude of serum ALT and AST activity elevation approximates the extent, but not the reversibility, of hepatocellular injury. Rather than clinical relevance being assigned to absolute values for ALT or AST activity (e.g., serum ALT activity of 200 IU/L is worse than 100 IU/L), the values should be assessed in terms of number of fold elevations from normal. Twofold to threefold elevations in serum ALT activity are associated with mild hepatocellular lesions, fivefold to tenfold elevations are seen with moderately severe lesions, and greater than tenfold increases suggest marked hepatocellular injury. ALT (and to a lesser extent AST) activity is also often increased by glucocorticoids in dogs, although to a lesser extent than ALP.

Serum enzyme activities that reflect new synthesis and release of enzyme from the biliary tract in response to certain stimuli are alkaline phosphatase (AP) and γ-glutamyltransferase (GGT). Bile retention (i.e., cholestasis) is the strongest stimulus for accelerated production of these enzymes. Unlike ALT and AST, AP and GGT are in low concentration in the cytoplasm of hepatocytes and biliary epithelium and are membrane-associated, so the fact that they simply leak out of damaged cells does not account for increased serum activity. Measurable AP activity is also detectable in nonhepatobiliary tissues of cats and dogs (including osteoblasts, intestinal mucosa, renal cortex, and placenta), but serum activity in healthy adult cats and dogs arises only from the liver, with some contribution by the bone isoenzyme in young, rapidly growing dogs and in kittens less than 15 weeks old. The renal form is mainly measurable in the urine, and the gut form has a very short half-life so is not usually measurable (although the steroid-induced isoenzyme of AP in dogs is believed to be an altered gut isoenzyme with a prolonged half-life). The half-life of feline AP is shorter than that of canine AP; thus serum activity is relatively lower in cats than in dogs with a similar degree of cholestasis, and, conversely, even mild elevations of AP in cats are clinically very significant. Markedly high serum AP activity of bone origin (mean total serum AP values more than fivefold higher than those in nonaffected individuals, with only the bone isoenzyme detected) was identified in certain healthy juvenile (7 months old) members of a family of Siberian Huskies (Lawler et al., 1996). This change is believed to be benign and familial and should be considered when results of serum AP activity are interpreted in this breed. A young, growing dog of any breed can have a mild increase in serum AP. Increased serum AP activity of unknown origin has also

been described in adult Scottish Terriers and is believed to be benign and possibly familial (Gallagher et al., 2006).

Certain drugs, the most common of which are anticonvulsants (specifically phenytoin, phenobarbital, and primidone) and corticosteroids, can elicit striking increases (up to hundredfold) in serum AP activity (and to a lesser extent GGT and also ALT activity) in dogs but not in cats. There usually is no other clinicopathologic or microscopic evidence of cholestasis (i.e., hyperbilirubinemia). Anticonvulsant drugs stimulate production of AP identical to the normal liver isoenzyme; GGT activity does not change. Pharmacologic levels of corticosteroids administered orally, by injection, or topically reliably provoke a unique AP isoenzyme that is separable from the others by electrophoretic and immunoassay techniques. This characteristic is useful when interpreting high total serum AP activity in a dog with subtle clinical signs suggestive of iatrogenic or naturally occurring hypercortisolism. The corticosteroid AP isoenzyme is a component of routine canine serum biochemistry profiles at several veterinary colleges and commercial laboratories. However, measurement of AP isoenzymes has been shown to be of limited usefulness either in dogs treated with phenobarbital (Gaskill et al., 2004) or in dogs with hyperadrenocorticism (Jensen et al., 1992). In the latter, it has a high sensitivity but very low specificity, so finding a low steroidinduced isoenzyme rules out hypercortisolism, but a high concentration of steroid-induced isoenzyme may be found in many disease other than hypercortisolism. Serum GGT activity rises similarly in response to corticosteroid influence but less spectacularly. Serum AP and GGT activities tend to be parallel in cholestatic hepatopathies of cats and dogs, although they are much less dramatic in cats. Simultaneous measurement of serum AP and GGT may aid in differentiating seemingly benign drug-induced effects from nonicteric cholestatic hepatic disease in dogs. Assessing serum AP and GGT activities together may also offer clues to the type of hepatic disorder in cats. Both enzymes are in low concentration in feline liver tissue compared with that in the canine liver and have short half-lives, so relatively smaller increases in serum activity, especially of GGT, are important signs of the presence of hepatic disease in cats. In cats a pattern of high serum AP activity with less strikingly abnormal GGT activity is most consistent with hepatic lipidosis (see Chapter 37), although extrahepatic bile duct obstruction (EBDO) must also be considered.

# TESTS TO ASSESS FUNCTION OF THE HEPATOBILIARY SYSTEM Serum Albumin Concentration

The liver is virtually the only source of albumin production in the body; thus hypoalbuminemia could be a manifestation of hepatic inability to synthesize this protein. Causes other than lack of hepatic synthesis (i.e., massive glomerular or gastrointestinal loss or bleeding) must be considered before ascribing hypoalbuminemia to hepatic insufficiency. Renal protein loss can be detected presumptively by routine urinalysis. Consistent identification of positive protein dip-

stick reactions, especially in dilute urine with inactive sediment, justifies further evaluation by at least measurement of random urine protein: creatinine ratio (normal ratio is <0.5 in cats and dogs). If proteinuria is ruled out, diseases that cause gastrointestinal protein loss should be considered; however, these diseases usually result in equivalent loss of globulins and thus panhypoproteinemia, although this is not invariably the case in inflammatory gastrointestinal disease wherein concurrent increase in gamma-globulins masks the gut loss. Conversely, although panhyproteinemia is reportedly not typical of hypoproteinemia of hepatic origin, globulin concentrations can be low in liver disease, particularly portosystemic shunts, because all plasma globulins except gamma globulins are made in the liver. In fact, globulin concentrations frequently are normal to increased in dogs and cats with chronic inflammatory hepatic disease. Because the plasma half-life of albumin is long in cats and dogs (8 to 10 days) and there must be loss of approximately 80% of functioning hepatocytes before hypoalbuminemia is expressed, the finding of hypoalbuminemia usually indicates severe chronic hepatic insufficiency. The exception to this is the hypoalbuminemia associated with a "negative acute phase" response in acute or acute-on-chronic inflammatory liver disease. Serum albumin can decrease when there is an increase in hepatic production of acute phase proteins in animals without hepatic insufficiency. Serum protein electrophoresis can help differentiate this condition from a true lack of hepatic function: Sevelius et al. (1995) showed that a low albumin concentration combined with a low concentration of acute phase proteins in electrophoresis indicated severe hepatic dysfunction with a poor prognosis, whereas hypoalbuminemia combined with normal or elevated acute phase proteins indicated a good prognosis. Hypoalbuminemia of any cause is unusual in cats, except in those with nephrotic syndrome. When interpreting serum protein concentrations, the clinician should remember that total protein values for young cats and dogs are lower than those for adults and that puppy serum albumin concentration is similar to that in adults, whereas kitten serum albumin concentration is lower than that in adult cats.

#### Serum Urea Nitrogen Concentration

Formation of urea as a means of detoxifying ammonia derived from intestinal sources takes place only in the liver. Despite this apparent advantage as a specific measure of hepatic function, serum urea concentration is commonly affected by several nonhepatic factors and the capacity of the liver to detoxify urea is so great that it is not noticeably reduced until severe, extensive end-stage liver disease ensues. Prolonged restricted protein intake because of complete anorexia or intentional reduction in protein intake for therapeutic purposes (e.g., chronic kidney disease; urate, cystine, or struvite urolithiasis) is the most common cause of low blood urea nitrogen (BUN) content. Prior fluid therapy and/ or marked polydipsia/poluria of nonrenal causes will also result in a decrease in BUN. As always, reference ranges should be considered for each species when interpreting

BUN values. For example, a BUN concentration of 12 mg/dl is well within normal limits for dogs but is subnormal for cats. If low BUN values are noted in a cat or dog with normal water intake and a good appetite for a diet with the appropriate protein content for the species (on a dry matter basis: 22% for dogs, 35% to 40% for cats), then the possibility of hepatic inability to convert ammonia to urea should be investigated.

#### Serum Bilirubin Concentration

Because of the large reserve capacity of the mononuclearphagocytic system and liver to process bilirubin (e.g., 70% hepatectomy will not cause jaundice), hyperbilirubinemia can occur only from greatly increased production or decreased excretion of bile pigment. Specific inborn errors of bilirubin uptake, conjugation, and excretion have not been documented in cats or dogs. Increased production of bilirubin from red blood cell destruction arises from intravascular or extravascular hemolysis and rarely from resorption of a large hematoma; hyperbilirubinemia also occurs in association with rhabdomyolysis in Greyhounds and other dog breeds. Under these circumstances in dogs, serum bilirubin concentrations are usually lower than 10 mg/dl. Values usually do not increase above 10 mg/dl unless there is a concurrent flaw in bilirubin excretion. This has been borne out clinically in studies of dogs with immune-mediated hemolytic anemia in which high liver enzyme activities are observed, even before treatment with corticosteroids, and moderately delayed bilirubin excretion has been documented. It has been proposed that cholestasis results from liver injury associated with hypoxia and in some cases due to early disseminated intravascular coagulation (DIC). Because increased production and decreased excretion of bilirubin occur in dogs with severe hemolysis, serum bilirubin concentrations therefore can be as high as 35 mg/dl. Icterus in cats with pure hemolytic disease is an inconsistent finding and mild if present; specific bilirubin concentrations associated with experimentally induced or naturally occurring hemolytic diseases in cats are not available.

Because nearly all diseases associated with hyperbilirubinemia in cats and dogs are characterized by a mixture of conjugated and unconjugated bilirubinemia, quantifying the two fractions by use of van den Bergh's test achieves little in discriminating primary hepatic or biliary disease from nonhepatobiliary disease in a clinical setting. This lack of benefit in using van den Bergh's test may relate to the time between onset of illness and examination, which is usually at least several days. Under conditions of acute massive hemolysis, the total serum bilirubin concentration may consist primarily of the unconjugated form initially. As hemolysis continues, the liver is able to take up and conjugate bilirubin, accounting for a combination of unconjugated and conjugated bilirubin.

Because red blood cell membrane changes are often a component of many primary hepatobiliary disorders, accelerated red blood cell destruction often contributes to hyperbilirubinemia. In such cases, there is strong clinicopathologic evidence of cholestasis (high serum AP and GGT activities with moderate to high ALT activity), and if there is anemia, it is mild and poorly regenerative. Hyperbilirubinemia is attributed primarily to hemolysis when there is moderate to marked anemia with strong evidence of regeneration (except in the first 1 to 3 days, when the response is less regenerative) and minimal changes in serum markers of cholestasis.

#### Serum Cholesterol Concentration

Total cholesterol concentration is included in serum chemistry profiles by many commercial laboratories but affords useful information for only a limited number of hepatobiliary diseases. High total cholesterol values are observed in cats and dogs with severe intrahepatic cholestasis involving bile ducts or EBDO because of impaired excretion of free cholesterol into the bile and subsequent regurgitation into the blood. Low total serum cholesterol concentrations have been noted in dogs with chronic severe hepatocellular disease and frequently in cats and dogs with congenital portosystemic shunts (PSS). It has been speculated that hypocholesterolemia is a sign of markedly altered intestinal absorption of (and increased use of) cholesterol for bile acid synthesis when the enterohepatic recirculation of bile acids is disturbed, as occurs with PSS. In other hepatobiliary diseases of cats and dogs, the total cholesterol values vary considerably within the reference range. Normal values in 4-week-old kittens are higher than those for adults; 8-week-old puppy reference ranges are the same as those for adults.

#### **Serum Glucose Concentration**

Hypoglycemia is an unusual event associated with hepatobiliary disease in dogs and especially in cats. Lost capacity to maintain normal serum glucose concentrations occurs in animals with acquired chronic progressive hepatobiliary disease when 20% functional hepatic mass or less is remaining. This inability to maintain normal serum glucose concentrations is presumably caused by the loss of hepatocytes with functioning gluconeogenic and glycolytic enzyme systems and impaired hepatic degradation of insulin. Hypoglycemia is often a near-terminal event in dogs with chronic progressive hepatobiliary disease. In striking contrast is the frequent observation of hypoglycemia in dogs with congenital PSS, particularly small-breed dogs. In PSS hypoglycemia may be due to an increase in circulating insulin concentration caused by reduced first pass metabolism in the liver, as observed in humans, but this has never been investigated in dogs. Hypoglycemia is also common as a paraneoplastic syndrome in dogs with large hepatocellular carcinomas and can be associated with production in insulin-like growth factor by the tumour (Zini et al., 2007). In either case, if hypoglycemia is identified and confirmed by repeating the test using sodium fluoride tubes if necessary, and if nonhepatic causes (functional hypoglycemia, sepsis, insulinoma, or other neoplasm producing an insulin-like substance, Addison's disease; see Chapter 53) are excluded, a primary hepatic tumor (e.g., hepatocellular carcinoma), a PSS, or severe generalized hepatopathy is suspected.

#### **Serum Electrolyte Concentrations**

Serum electrolyte determinations facilitate supportive care of cats and dogs with hepatobiliary disease but give no particular hints as to the character of the disorder. The most common abnormality is hypokalemia, which is attributed to a combination of excessive renal and gastrointestinal losses, reduced intake, and secondary hyperaldosteronism in dogs and cats with severe chronic hepatobiliary disease. Metabolic alkalosis, presumptive evidence of which might be abnormally high serum total carbon dioxide content confirmed by blood gas analysis, is usually caused by overzealous diuretic therapy in dogs with chronic hepatic failure and ascites. Hypokalemia and metabolic alkalosis potentiate each other and may also worsen signs of hepatic encephalopathy (HE) by promoting persistence of readily membrane-diffusible ammonia (NH<sub>3</sub>).

#### Serum Bile Acid Concentrations

Recent validation of rapid, technically simple methods for SBA analysis in cats and dogs has provided a sensitive, variably specific test of hepatocellular function and the integrity of the enterohepatic portal circulation. "Primary" bile acids (i.e., cholic, chenodeoxycholic) are synthesized only in the liver, where they are conjugated with various amino acids (primarily taurine) before secretion into the bile. Bile is stored in the gallbladder, where it is concentrated until, under the influence of cholecystokinin, it is released into the duodenum. After facilitating fat absorption in the small intestine, the primary bile acids are efficiently absorbed into the portal vein and returned to the liver for reuptake and resecretion into the bile. A small percentage of primary bile acids that escapes resorption is converted by intestinal bacteria to "secondary" bile acids (i.e., deoxycholic, lithocholic), some of which are also resorbed into the portal circulation. Absorption of bile acids by the intestine is extremely efficient, but hepatic extraction from portal venous blood is not. This accounts for small concentrations of cholic, chenodeoxycholic, and deoxycholic acids that are released into the peripheral blood of healthy cats and dogs in the fasting state (total <5 µmol/L by enzymatic method and 5 to 10 µmol/L by radioimmunoassay [RIA]). During a meal a large load of bile acids is delivered to the intestine and portal circulation for recycling; postprandial values in normal dogs and cats may increase up to threefold to fourfold over fasting values (15 µmol/L with the enzymatic method for cats and dogs; 25 μmol/L with the RIA method for dogs). Normal values for juvenile animals are similar to adult reference ranges. Abnormally high fasting and/or postprandial SBA concentrations reflect disturbance in hepatic secretion into the bile or at any point along the path of portal venous return to the liver and hepatocellular uptake. Low SBA concentrations may be attributable to small intestinal (ileal) malabsorption of bile acids but might be difficult to interpret because both fasting and postprandial SBA concentrations may not be measurable in healthy animals.

The standard way to assess SBA concentrations is outlined in Box 36-1. Collective experience indicates that the



BOX 36-1

Summary of Techniques for Bile Acid Stimulation Test and Postprandial Ammonia Challenge Test

#### **Bile Acid Stimulation Test**

Collect a 3-ml blood sample in a serum tube after the animal was fasted for 12 hours.

Feed a small amount of food that is normal in fat content (approximately 27% fat [dry matter basis] in dogs).

Collect another 3-ml blood sample in a serum tube 2 hours after the meal.

#### Postprandial Ammonia Challenge Test

Collect a 3-ml blood sample after the animal was fasted for 12 hours.

Feed an amount of food corresponding to 25% of the dog's daily metabolic energy requirement.

Collect another 3-ml blood sample in a serum tube 6 hours after the meal.

likelihood of precipitating an episode of HE during this part of the test is extremely low, even in predisposed animals. After the serum is harvested, the samples may be refrigerated for several days or frozen almost indefinitely before assay. The stability of the blood sample is one of the major advantages over the much more labile serum ammonia test.

Studies of SBAs have confirmed their value in detecting clinically relevant hepatobiliary disease requiring definitive diagnostic testing in cats and dogs, especially in anicteric animals with equivocal clinical signs and unexplained high liver enzyme activity. There continues to be controversy as to whether a fasting or postprandial value alone is sufficient or whether fasting and postprandial measurements are required. If only one sample can be obtained (and the animal will eat or can tolerate being force-fed a small meal), the postprandial value is most useful to determine the presence or absence, but not the type, of clinically relevant hepatobiliary disease in most cats and dogs. Current recommendations state that for animals suspected of having acquired hepatobiliary disease, biopsy is needed when postprandial SBA concentration using the enzymatic method exceeds 20 μmol/L in cats and 25 μmol/L in dogs, although other authors (particularly in the United Kingdom) suggest that SBA between 20 and 40 µmol/L in dogs represents a grey area (Hall et al., 2005). Elevations in this region have been seen with secondary hepatopathies (particularly hyperadrenocorticism) and with small intestinal bacterial overgrowth because of reduced hepatic clearance of deconjugated bile acids. Therefore the authors would recommend a liver biopsy with a higher cut-off for postprandial bile acids of 40 μmol/ L. No pattern of preprandial and postprandial values is pathognomonic for any particular hepatic disorder, although it is safe to make certain generalizations. Magnitude of elevation above 20  $\mu$ mol/L in cats and 25  $\mu$ mol/L in dogs roughly correlates with the severity, but not the reversibility, of the hepatobiliary disorder, although with PSS, the magnitude of elevation does not correlate with the degree of shunting or severity of clinical signs. The change between the fasting value and the postprandial value likely corresponds to portosystemic shunting, either microscopic (intrahepatic) or macroscopic. There is so much overlap in fasting and postprandial SBA patterns among primary hepatobiliary diseases that no particular statement can be made regarding the specific causative hepatobiliary disease. Occasionally, fasting SBA levels are higher than postprandial levels, which signifies nothing more than occasional, normal, spontaneous gallbladder contraction in fasting. In general, secondary hepatic diseases cause more modest hepatobiliary dysfunction (SBA values <100  $\mu$ mol/L).

For the diagnosis of congenital PSS, fasting and postprandial SBA determinations are recommended to enhance detection ability because it is relatively common for fasting values to be well within normal limits and for postprandial values to be as high as tenfold to twentyfold higher than normal postprandial values.

Now that simplified methods for SBA measurement have been developed (i.e., enzymatic, RIA) and are accessible, determination of total SBA has become a convenient, practical test of hepatobiliary function in cats and dogs. Some reference laboratories use an adapted enzymatic method, a commercial enzymatic kit (Enzabile; Nyegaard and Co., Olso, Norway), or a commercial RIA (Conjugated Bile Acids Solid Phase Radioimmunoassay Kit 125I; Becton Dickinson, Orangeburg, N.Y.). Each yields comparable diagnostic results, although the sample size needed for the RIA assay is quite small (50 µl) compared with the enzymatic method (400 to 500 µl). Because the measurement of fasting and postprandial SBA concentrations assesses the same functions as the ammonium chloride (NH<sub>4</sub>Cl) tolerance test without potentially dangerous consequences, it is the preferred test. As with any specially requested test, the laboratory chosen should use methods verified for clinical use in the target species and be able to provide reference ranges.

A benchtop "SNAP" test for bile acids has recently become available from IDEXX Laboratories (see http://www.idexx.com/animalhealth/analyzers/vetlabnotes/2005snapreader.jsp). The disadvantage of the SNAP test is that it has a low cut-off, which means that it does not differentiate secondary from primary hepatobiliary disease.

Several factors may affect SBA values and therefore their interpretation. One aspect of the SBA challenge test that has not been standardized is the feeding step. The ideal quantity and composition of the test meal have not been determined. Size of the test meal and therefore consumption of the entire meal or only part of the meal may affect gastric emptying. Delayed gastric emptying could cause the peak SBA concentration to occur more than 2 hours later. Hastened or delayed intestinal transit time or the presence of intestinal disease (especially of the ileum) may also impede and blunt peak absorption of the test meal. It is likely that fat content of the test meal is important because fat is the primary stimulus for the small intestinal mucosa to secrete cholecystokinin, which

causes gallbladder contraction. Expulsion of bile during periodic physiologic gallbladder contraction between meals may complicate interpretation of the fasted sample result. Lipemia of the sample can seriously affect the validity of the test, particularly on heparinized blood. For this reason, it is far preferable to use serum, both for the external samples and for the snap test.

Several questions remain to be answered regarding the clinical use of SBA measurement in cats and dogs. Investigation of individual SBA profiles in cats and dogs with various hepatobiliary diseases has provided interesting information but no clear and specific profile for any one disease. Can sequential SBA values be used to more precisely monitor a cat's or dog's progress? Until this and other questions are answered, use of SBA analysis is limited to measuring total serum values as a sensitive and relatively specific screening test for the presence or absence of clinically significant hepatobiliary disease. Additional diagnostic testing must always follow to identify the specific cause.

#### **Urinary Bile Acid Concentrations**

Determination of bile acids accumulating in urine over time can be used to assess hepatobiliary function. Urine bile acids are believed to reflect average serum bile acid concentrations during the interval of urine formation. Expression of urine bile acid concentrations as a ratio with the urine creatinine concentration eliminates the influence of urine concentration and flow. Random urine sampling for bile acid determination does not require attending to the timing of an enterohepatic challenge or obtaining a sample after withholding food. In recent studies urinary bile acid concentrations were increased in dogs and cats with hepatobiliary disease and portosystemic vascular anomalies, compared with dogs and cats with nonhepatic disorders (except for hepatic neoplasia in dogs; Balkman et al., 2003; Trainor et al., 2003). The urine nonsulfated bile acid: creatinine ratio and the urine sulfated plus nonsulfated bile acid: creatinine ratio positively correlated with serum bile acid test results and had similar overall diagnostic performance and substantially higher (dogs) or similar (cats) specificity, compared with the serum bile acid test, and are recommended. The urine sulfated bile acid: creatinine ratio had lower sensitivity in dogs and cats, compared with the serum bile acid test.

#### **Plasma Ammonia Concentration**

One test that is not included in a standard screening battery of tests but is available through reference or human hospital laboratories is plasma ammonia concentration. Fasting plasma ammonia can be measured in any cat or dog with historic or physical examination findings suggestive of HE. Signs of HE (see Box 35-2), whether they have a congenital or acquired basis, appear the same. Quantifying plasma ammonia concentration not only can confirm HE, although normal fasting values in animals with hepatobiliary disease are relatively common, but can also provide baseline data and help in evaluating response to treatment. However, SBA

values (particularly postprandial) provide very similar information. Some investigators have suggested that arterial ammonia concentrations may more accurately represent blood ammonia status in dogs with hepatobiliary disease than venous measurements because skeletal muscle can metabolize ammonia. High plasma ammonia concentration usually indicates reduced hepatic mass available to process ammonia and/or the presence of portosystemic shunting, which disrupts presentation of ammonia to the liver for detoxification. However, ammonia is very labile in the blood sample and, for example, can be falsely elevated if the blood sample is taken in an environment contaminated with urine. Sample handling has to be undertaken with caution, and some benchtop analyzers are inaccurate, particularly in the moderately elevated range. For these reasons, SBAs are often a preferred test. The exception to this would be an animal with suspected hepatic encephalopathy and concurrent cholestasis. As outlined in the preceding paragraphs, bile acid concentrations will be high in cholestasis (because they are excreted in the bile) independent of any reduction in liver function or shunting. Measuring blood ammonia in these circumstances will give useful additional information about potential shunting and HE.

In a recent study the 12-hour fasting plasma ammonia concentration had higher sensitivity and specificity than the 12-hour fasting bile acid concentration for detecting portosystemic shunting in a general population of dogs and in dogs with liver disease (Gerritzen-Bruning et al., 2006). However, a bile acid stimulation test (fasting and 2-hour postprandial bile acid) has a much higher sensitivity for detecting PSS than a single fasting bile acid, and a single postprandial bile acid concentration is likely as sensitive as a fasting ammonia concentration, although the authors did not test this.

Although reference ranges vary among laboratories, fasting plasma ammonia values for normal dogs are typically 100 mg/dl or less and 90 mg/dl or less for normal cats. At least 6 hours of fasting should precede sample collection. Samples must be collected into iced ammonia-free heparinized tubes and spun immediately in a refrigerated centrifuge. Plasma must be removed within 30 minutes so that values will not be spuriously elevated by hemolysis because red blood cells contain two to three times the ammonia concentration of plasma. To obtain accurate values, feline plasma can be frozen at -20°C and assayed within 48 hours; canine plasma must be assayed within 30 minutes.

If signs are compatible with HE at the time of sample collection, a single fasting sample will suffice. If there are no signs of HE and results of other tests are equivocal, a post-prandial challenge test may be performed (see Box 36-1). The older ammonium chloride challenge tests (either oral or rectal) are contraindicated because of the significant potential for either test to trigger a severe encephalopathic crisis in the patient. The postprandial ammonia test is a safer test and has a 91% sensitivity for portosystemic shunting but only a 31% sensitivity for diffuse hepatocellular disease (Walker et al., 2001).

#### **Plasma Protein C Activity**

Plasma protein C activity was recently evaluated as a marker of hepatobiliary disease in dogs. Protein C is an anticoagulant protein that is synthesized in the liver and circulates as a plasma zymogen. Low protein C activity has been associated with thrombotic disorders in humans and animals. Low protein C activity has also been documented in dogs with acquired and congenital hepatobiliary disorders, and dogs with PSS appear to develop the lowest protein C activity. In a recent study by Toulza et al. (2006), protein C acivity was significantly lower in dogs with congenital or acquired portal systemic shunts, compared with dogs without PSS. Plasma protein C activity improved or normalized after surgery for the shunt. These findings suggest that plasma protein C activity reflects the adequacy of hepatoportal perfusion in dogs and that protein C activity may prove useful as a means to monitor improvement of hepatic-portal perfusion after ligation of portosystemic vascular anomalies. Plasma protein C activity may also help differentiate dogs with intrahepatic portal vein hypoplasia from those with portal systemic vascular anomaly (plasma protein C activity ≥70% versus <70%, respectively).

#### **URINALYSIS**

Common findings in urinalysis consistent with hepatobiliary disease include excessive bilirubinuria in a nonanemic dog (2+ in urine of specific gravity <1.025), presence of bilirubin in the urine of cats, and ammonium biurate crystalluria in properly processed urine specimens (Fig. 36-1). In dogs excessive bilirubinuria may precede the onset of hyperbilirubinemia and jaundice. Small numbers of bilirubin crystals may be found in concentrated urine specimens from normal dogs and ammonium biurate crystals are also occasionally found in normal animals and also in Dalmatian dogs with a defect in urate metabolism (see Chapter 46) and therefore are not pathognomonic for PSS. Hyperammonemia combined with excess uric acidemia from diminished hepatic

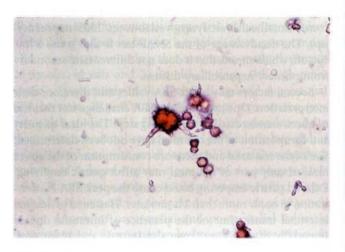


FIG 36-1
Ammonium biurate crystals in the urine of a dog with a congenital portosystemic shunt.

conversion to allantoin exceeds the renal threshold and favors precipitation of crystals, especially in alkaline urine. Their presence in the urine may fluctuate, but alkalinizing the urine specimen with a few drops of sodium or potassium hydroxide may increase the likelihood of identifying ammonium biurate crystals during sediment examination.

Measurement of urinary urobilinogen by dipstick analysis has traditionally been used to assess the patency of the extrahepatic biliary system. So many factors influence detection of urobilinogen in the urine (e.g., intestinal flora and transit time, renal function, urine pH and specific gravity, exposure of the urine specimen to light) that the test is now considered to be of minimal value in diagnosing EBDO. If urine samples are obtained serially and processed properly, repeated absence of urobilinogen suggests, but is not diagnostic of, complete EBDO.

Consistently dilute urine (specific gravity as low as 1.005) may be a feature of congenital and acquired PSS and severe hepatocellular diseases because of the associated polydipsia/polyuria and hypercortisolism, as discussed in Chapter 35. Urine specific gravity must also be interpreted in light of concurrent drug therapy, such as administration of diuretics, corticosteroids, or anticonvulsants.

#### **FECAL EVALUATION**

Fecal specimen analysis rarely provides useful information in the evaluation of a dog or cat with suspected hepatobiliary disease, except for a change in appearance associated with two specific conditions. Absence of fecal pigment (acholic feces; see Fig. 35-6) and steatorrhea are consequences of chronic complete EBDO, and dark, orange-colored feces reflect increased bilirubin production and excretion after marked hemolysis or rhabdomyolysis. It should also be noted that gastrointestinal ulceration is a serious and important complication of portal hypertension, particularly in dogs (see Chapter 39), so the clinician should always be alert to the development of melena in a dog with chronic liver disease.

#### ABDOMINOCENTESIS/FLUID ANALYSIS

If abdominal fluid is detected during physical examination, abdominal radiography, or ultrasonography, a sample must always be obtained for analysis. For moderate to large volume effusion, simple needle paracentesis is sufficient to obtain 5 to 10 ml of fluid for gross inspection; determination of protein content; cytologic evaluation; and, in selected cases, special biochemical analysis. Larger volumes are removed using an over-the-needle-style catheter with extension tubing or a needle with attached tubing (E-Z infusion set) if clinical signs secondary to fluid accumulation are present (e.g., dyspnea) or if removal of abdominal fluid is part of the treatment (e.g., bile peritonitis). Removal of a significant volume of abdominal fluid for clinical reasons should be avoided unless it is absolutely necessary because doing so often causes a precipitous decrease in serum protein concentrations in animals with liver disease owing to the inability of the liver to replace proteins removed in the fluid. It is

preferable in cases other than peritonitis to remove fluid gradually, using diurctics. In cases in which large volume fluid removal is necessary (e.g., for dyspnea), concurrent administration of fresh frozen plasma or a colloid solution is essential. In dogs with chronic hepatic failure and sustained intrahepatic portal hypertension, abdominal fluid is usually a modified transudate with moderate nucleated cell count and protein content (Table 36-1). A pure transudate with low cell count (<2500 cells/µl) and protein concentration (<2.5 g/dl), and a clear, minimally colored appearance is found when the dog is hypoproteinemic. Abdominal fluid in dogs with intrahepatic postsinusoidal venous obstruction (e.g., venoocclusive disease) or posthepatic venous obstruction (e.g., any cause of right-sided heart failure) can be any color but is typically red- or yellow-tinged and is classified as a modified transudate. Feline infectious peritonitis fluid and neoplastic effusions are also commonly classified as modified transudates or nonseptic exudates. Bile peritonitis also results in an exudate, which is initially sterile but can become septic with time. With neoplasia, effusions can occasionally be chylous or even hemorrhagic, and the latter can also be seen in amyloidosis as a result of rupture of the liver capsule. Reactive mesothelial cells can be mistaken for neoplastic cells, emphasizing the need for experience in evaluating cytologic specimens. Exudates have high cell counts (>20,000 cells/µl) and protein content (>2.5 g/dl) and, on the basis of whether the inflammatory cells look toxic or contain ingested bacteria, are further classified as septic or nonseptic. Fluid analysis provides additional clues to the origin of hepatobiliary disease and must not be overlooked. A guide to interpreting fluid analysis results is given in Table 36-1.

#### **COMPLETE BLOOD COUNT**

There are few changes in blood cells that suggest hepatobiliary disease. Most are changes in erythrocytes associated with fragmentation or changes in cell size or membrane composition (Fig. 36-2). Microcytosis (mean cell volume [MCV] <60 fl in canine breeds other than the Japanese Akita or Shiba Inu) with normochromia or slight hypochromia (mean cell hemoglobin concentration: 32 to 34 g/dl) is a rather common finding in dogs with congenital PSS (≥60%); it is less common in cats with congenital PSS (≤30%). Most affected animals are not anemic. The cause of microcytosis, which has also been observed with less frequency in dogs with chronic hepatic failure and acquired PSS, is chelation of iron within the liver rather than absolute iron deficiency; therefore iron supplementation does not help. However, the change in the size of red blood cells is reversible upon restoration of portal blood flow. If anemia is also present, microcytosis must be distinguished from anemia of inflammatory disease, which can occasionally cause small red blood cells and relative iron deficiency, or from iron deficiency anemia associated with chronic gastrointestinal blood loss (see Chapter 83).

Strongly regenerative anemia, with macrocytosis, high reticulocyte count, and normal to slightly increased serum



TABLE 36-1

Characteristics of Abdominal Effusion in Hepatobiliary Disease

	APPEARANCE	CELL COUNT	PROTEIN CONTENT	SPECIFIC GRAVITY	EXAMPLE(S)
Pure transudates	Clear, colorless	<1500/μΙ	<2.5 g/dl	<1.016	Chronic hepatic failure with marked hypoalbuminemia
Modified transudates	Serosanguineous, amber	<7000/μΙ	≥2.5 g/dl	1.010-1.031	Chronic hepatic failure, right-sided heart failure, pericardial disease, caval syndrome, Budd-Chiari-like syndrome, intrahepatic portal vein hypoplasia, chronic portal vein thrombosis, feline infectious peritonitis [some cases], neoplasia (some cases]
<b>Exudates</b> Septic	Cloudy; red, dark yellow, green	>7000/μl	≥2.5 g/dl	1.020-1.031	Perforated duodenal ulcer, bile peritonitis (fluid bilirubin concentration exceeds serum bilirubin concentration)
Nonseptic	Clear; red, dark yellow, green	>7000/μl	≥2.5 g/dl	1.017-1.031	Feline infectious peritonitis, neoplasia with serosal involvement, ruptured hemangiosarcoma, early bile peritonitis
Chylous effusions	Opaque, white to pink ("strawberry milkshake")	Variable; usually 1000- 10,000/μl	Variable; 2.5- 6.5 g/dl	1.030-1.032	Neoplasia (some cases); diseases obstructing lymphatic drainage
Hemorrhagic effusions	Red	Variable; usually 1500 to 1000/µl	Usually >3.0 g/dl	<1.013	Neoplasia (some cases); amyloidosis with hepatic capsule rupture; ruptured hemangiosarcoma

protein concentration in a jaundiced dog, especially if spherocytes are also identified, indicates hemolytic anemia and increased bilirubin formation as the cause of jaundice. Cats and dogs with hemolytic anemia typically also have high serum liver enzyme activities and bile acid concentrations, pointing to hepatic consequences developing secondary to the effects of marked hemolysis, such as hypoxia and thromboembolism.

Certain red blood cell morphologic changes are consistent with serious hepatobiliary disease and are related to alterations in lipoprotein metabolism and irregularities in red blood cell membrane structure. Acanthocytes, leptocytes, and codocytes (target cells) are good examples (see Fig. 36-2). Poikilocytosis of unknown pathogenesis is a consistent finding in cats with congenital PSS and occasionally with other hepatobiliary diseases; cats with chronic hepatobiliary disease frequently have Heinz bodies in their red blood cells. Fragmented red blood cells or schistocytes constitute an expected finding in animals with DIC; hemangiosarcoma is considered when an inappropriate number of

nucleated red blood cells is also detected. Mild to moderate nonregenerative anemia is common in cats with many different illnesses, including those of the hepatobiliary tract.

Few changes in the leukon are expected in cats or dogs with hepatobiliary disease, except when an infectious agent is present as the initiating event (histoplasmosis, bacterial cholangitis, or leptospirosis in dogs); where there is concurrent pancreatitis, which is particularly common in cats (see Chapter 40); or when infection has complicated a primary hepatobiliary disorder (e.g., gram-negative sepsis in a dog with cirrhosis, septic bile peritonitis). Neutrophilic leukocytosis is likely in such cases, whereas pancytopenia is typical of disseminated histoplasmosis and severe toxoplasmosis in cats and of early infectious canine hepatitis.

#### **COAGULATION TESTS**

Clinically relevant coagulopathies are unusual in cats and dogs with hepatobiliary disease except for those with acute hepatic failure (including acute hepatic lipidosis in cats or hepatic lymphoma in both species), complete EBDO, or

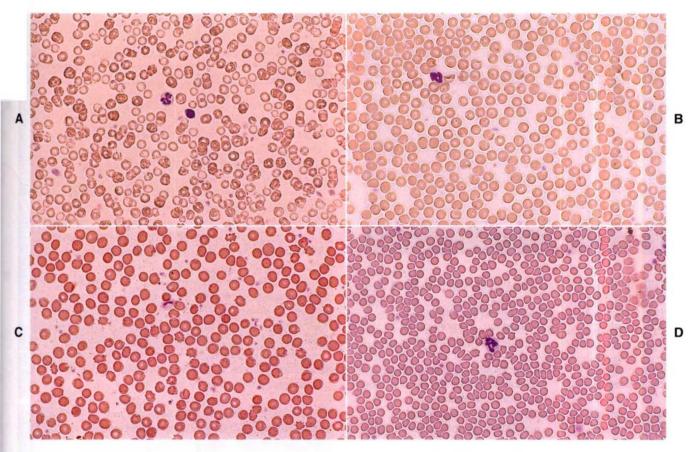


FIG 36-2

Erythrocyte morphologic changes often associated with hepatobiliary disease in cats and dogs (Wright-Giemsa stain). **A,** Microcytic red blood cells (mean corpuscular volume [MCV] = 45 fl) from dog with congenital portosystemic shunt; compare the microcytic red blood cells with the size of a nearby normal small lymphocyte 6 to 9  $\mu$ m in diameter. **B,** Normal canine red blood cells (MCV = 70 fl) for comparison. **C,** Acanthocytes from dog with severe chronic hepatic passive congestion. **D,** Poikilocytes from cat with cholangitis.

active DIC. It is more common to have subtle prolongation of activated partial thromboplastin time (APTT; 1.5 times normal), abnormal fibrin degradation products (10 to 40 or higher), and variable fibringen concentration (<100 to 200 mg/dl) in cats and dogs with severe parenchymal hepatic disease. Elevated D-dimers are common in patients with liver disease and do not always indicate DIC in these cases. It has been proposed that nonspecific elevation can occur in liver disease as a result of reduced clearance by the liver. Platelet numbers may be normal or low; mild thrombocytopenia (130,000 to 150,000 cells/µl) is usually associated with splenic sequestration or chronic DIC. More severe thrombocytopenia (100,000 cells/1) is expected in acute DIC or decompensated chronic DIC. Some animals with severe hepatic disease and relatively unremarkable routine coagulation test results have high serum activity of proteins induced by vitamin K antagonism (PIVKA) that could impart bleeding tendencies. Primary or metastatic cancer of the liver could also cause coagulopathy unrelated to loss of hepatocellular ability to make or degrade coagulation proteins.

A summary of laboratory tests for cats and dogs with hepatobiliary disease and interpretation of their results is given in Table 36-2.

#### **DIAGNOSTIC IMAGING**

#### **SURVEY RADIOGRAPHY**

Radiographic evaluation of the abdomen is used to complement physical examination findings and to confirm suspicions regarding the character and location of the hepatobiliary disease suggested by results of clinicopathologic examination. Survey radiographs provide subjective information regarding the size and shape of the liver (see Table 35-1). Optimally, the animal should have an empty gastrointestinal tract at the time the radiographs are obtained. In the normal dog and cat in right lateral recumbency, the gastric axis is parallel to the ribs at the tenth intercostal space, and the caudoventral border of the liver (the left lateral liver lobe) appears sharp; the image is made possible by the con-



**TABLE 36-2** 

Summary of First- and Second-Line Clinicopathologic Tests Useful in the Diagnosis of Hepatobiliary Disease

SCREENING TEST	PRINCIPLE EXAMINED	COMMENTS
Serum ALT, AST	Integrity of liver cell membranes;	Degree of increase roughly correlates with number of
activities	escape from cells	hepatocytes involved but not severity of disease
Serum AP, GGT activities	Reactivity of biliary epithelium to various stimuli; increased synthesis and release	Increase associated with intrahepatic or extrahepatic cholestasis or drug effect (dogs only): corticosteroids, anticonvulsants (AP only, not GGT)
Serum albumin concentration	Protein synthesis	Rule out other causes of low concentration (glomerular or intestinal loss); low value indicates ≥80% overall hepatic function loss or negative acute phase response
Serum urea concentration	Protein degradation and detoxification	With low values, rule out prolonged anorexia; dietary protein restriction; severe PU/PD; urea cycle enzyme deficiency (rare); congenital PSS; severe, acquired chronic hepatobiliary disease
Serum bilirubin concentration	Uptake and excretion of bilirubin	Rule out marked hemolysis first; if PCV is normal, intrahepatic or extrahepatic cholestasis is present
Serum cholesterol concentration	Biliary excretion, intestinal absorption, integrity of the enterohepatic circulation	High values compatible with severe cholestasis of any kind; low values suggest congenital PSS; anticonvulsant drug-induced change; severe, acquired chronic hepatobiliary disease; or severe intestinal malassimilation
Serum glucose concentration	Hepatocellular gluconeogenic or glycolytic ability; insulin and other hormone metabolism	Low values indicate severe hepatocellular dysfunction, PSS, or presence of a primary liver tumor
Plasma ammonia concentration	Integrity of the enterohepatic circulation, hepatic function and mass	High fasting or postprandial values suggest congenital or acquired PSS or acute hepatocellular inability to detoxify ammonia to urea (massive necrosis)
Serum bile acid concentrations	Integrity of the enterohepatic circulation, hepatic function and mass	High fasting or postprandial values compatible with hepatocellular dysfunction, congenital PSS, or loss of hepatic mass. Elevated in cholestasis independent of hepatocellular dysfunction or shunting so rule this out first
Coagulation profile	Hepatocellular function, adequacy of vitamin K absorption and stores	Abnormal values may indicate marked hepatocellular dysfunction, acute or chronic DIC, complete EBDO

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; GGT, Yglutamyltransferase; PU/PD, polyuria/polydipsia; PSS, portosystemic shunting; PCV, packed cell volume; DIC, disseminated intravascular coagulation; EBDO, extrahepatic bile duct abstruction.

trasting fat-filled falciform ligament (Fig. 36-3). In dog breeds with narrow, deep chests, the entire liver shadow may be contained within the caudal rib cage. In dogs with wide, shallow thoracic conformation, the liver may extend slightly beyond the costal arch. In the ventrodorsal view the borders of the liver are defined by the cranial duodenum and the gastric fundus; in this view the gastric shadow is perpendicular to the spine. This view is less useful for assessing liver size unless it is markedly and asymmetrically enlarged. Immature animals have a relatively larger liver than do adults. The gallbladder and extrahepatic biliary tree are not visible separately radiographically in healthy animals.

Survey radiography is of minimal to no benefit if there is moderate to marked abdominal effusion because the similar radiographic opacities of the liver and fluid preclude distinction of liver size and shape except by indirect assessment (e.g., malposition of a gas-filled stomach and duodenum; Fig 36-4). However, because abdominal fluid increases ultraso-

nographic contrast, this is the imaging modality of choice in animals with ascites. Poor abdominal detail in emaciated or very young animals lacking abdominal fat stores also makes detection of subtle hepatic changes difficult.

In cats and dogs with generalized hepatomegaly, the liver extends beyond the costal arch; it causes displacement of the gastric axis and pylorus caudally and dorsally in the lateral projection and shifting of the gastric shadow caudally and to the left in the ventrodorsal view (see Fig 36-3). In addition, the edges of the liver in the lateral view may appear rounded (see Fig. 36-3). Occasionally, the spleen and liver cannot be differentiated when they are in direct contact, as seen in the right lateral view. A ventrodorsal view would help to determine the size, shape, and position of each organ. Increased intrathoracic volume associated with deep inspiration, severe pleural effusion, or overinflation of the lungs may result in caudal displacement of the liver, giving the erroneous impression of hepatomegaly using other radiographic criteria.

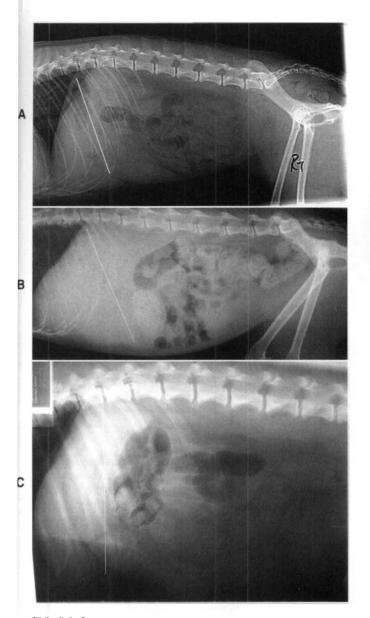
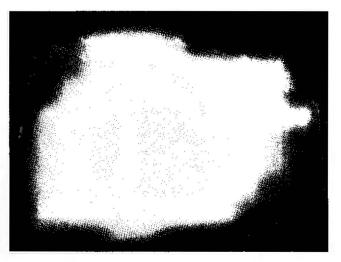


FIG 30-3

Lateral abdominal radiographs demonstrating gastric axis (white line) as an indication of liver size. A, Lateral abdominal radiograph of a normal cat with normal liver size. B, Lateral abdominal radiograph of a cat with diffuse hepatic amyloidosis demonstrating hepatomegally and caudal displacement of the gastric axis. C, Lateral abdominal radiograph of a middle-aged English Springer Spaniel with cirrhosis demonstrating microhepatica and cranial displacement of the gastric axis. (Radiographs courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

Because the liver may be contained entirely within the rib cage in normal cats and dogs, microhepatia is more difficult to recognize than hepatomegaly. Changes in the angle of the gastric fundus in the right lateral projection (see Fig. 36-3) could indicate a small hepatic shadow if the angle is more upright or perpendicular to the spine and especially if the stomach seems rather close to the diaphragm. The liver may

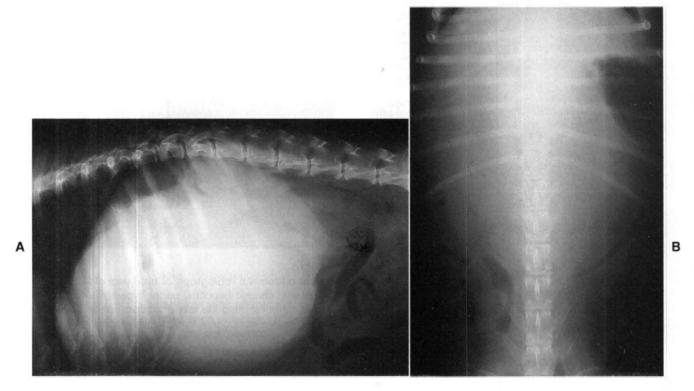


Lateral abdominal radiograph of an 8-year-old Bearded Collie with chronic hepatitis, portal hypertension, and ascites demonstrating the loss of abdominal detail associated with free abdominal fluid, which renders radiography unhelpful. (Radiograph courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

also seem small in animals with traumatic diaphragmatic hernia and herniation of liver lobes into the thorax or in those with congenital peritoneopericardial hernia.

Focal hepatic enlargement is indicated by displacement of organs adjacent to the affected lobe. The most common radiographically detectable focal hepatic enlargement is that of the right lateral lobe, an example of which is shown in Fig. 36-5. In this case the body and pyloric regions of the stomach are shifted dorsally (lateral view) and to the patient's left (ventrodorsal view); the gastric fundus remains in normal position. Shifting of the stomach to the left is normal in cats and should not be mistaken for right hepatomegaly. If the left lateral lobe or lobes are enlarged, the gastric fundus moves to the left and caudally; the lesser curvature of the stomach may appear indented. Primary or metastatic neoplasia, hyperplastic or regenerative nodules, and cysts most commonly account for focal hepatic enlargement or for irregular liver margins without enlargement. If the gallbladder is massively enlarged because of EBDO, it may mimic a right cranial abdominal mass or an enlarged, rounded liver lobe. Changes in hepatic radiographic opacity are rare and are usually associated with hepatic or biliary tract infection caused by gas-forming bacteria (patchy and/or linear areas of decreased opacity) or mineralization (focal or diffuse spots of mineralization or mineralized biliary calculi).

With the advent of ultrasonography, contrast radiographic procedures are seldom needed to confirm the presence of hepatic masses, cholelithiasis, EBDO, congenital PSS, and other structural diseases. The contrast study that is still necessary to localize some types of congenital PSS and is achievable in private practice is portal venography. Acceptable approaches for this technique are splenoportography,



Lateral (A) and ventrodorsal (B) abdominal radiographs of a 9-year-old spayed female mixed-breed dog with a hepatocellular carcinoma enlarging the right lateral liver lobe. The dog was also severely hypoglycemic.

operative mesenteric portography, and operative splenoportography. The two operative procedures require general anesthesia and a small abdominal incision; however, little sophisticated equipment is needed, and the procedures are associated with few complications. A 22-gauge catheter is placed in the splenic vein or a mesenteric vein (Fig. 36-6), and the resting portal venous pressure is measured with a water manometer (N = 6 to 13 cm  $H_2O$ ). Portal pressure is measured as soon as possible in the procedure because prolonged anesthesia may complicate its interpretation. An injection of iodine-based contrast medium at a dose of 0.5 to 1 ml/kg is then quickly made. Lateral and possibly ventrodorsal and oblique radiographs are made at the end of the injection. Contrast medium given to a normal cat or dog should flow into the portal vein, enter the liver, and branch multiple times, opacifying the extrahepatic and intrahepatic portal vasculature. Diversion of the contrast medium into the systemic circulation indicates PSS (Fig. 36-7). Measurement of portal pressure and a liver biopsy can be performed during the operative techniques; they are required to distinguish acquired PSS from congenital PSS, which is essential to rendering an accurate prognosis and developing the correct treatment plan. As a general rule, cases of congenital PSS are usually single whereas acquired PSS are multiple, so the mesenteric portography may suggest a diagnosis. It may be necessary to repeat the contrast study after congenital PSS ligation if there is concern about the adequacy of the intrahepatic portal vasculature. In addition, it has been shown that the degree of intrahepatic portal vessel opacification on post-ligation portography is predictive for outcome (Lee et al., 2006).

#### **ULTRASONOGRAPHY**

Abdominal ultrasonagraphy (US) is the preferred diagnostic modality for evaluating the hepatobiliary system in dogs and cats. Operating on the principle that a pulse of sound (echo) can be reflected when it passes through the interface between two different materials, US can detect differences between homogeneous liquids of low echogenicity, such as blood and bile, and more heterogeneous echogenic structures made up of several soft tissues. Whereas abdominal effusion obscures abdominal detail on survey radiography, it enhances the ability of US to detect abnormalities (Fig. 36-8). However, bone and gas-filled organs reflect the sound beam completely (acoustic shadowing) so that structures beneath cannot be imaged by US. The procedure does not require anesthesia, but the patient must be still, and good contact between the transducer and abdominal skin must be ensured by clipping the hair coat and applying acoustic coupling gel. Animals are usually positioned in dorsal or lateral recumbency. The hepatic parenchyma, gallbladder, large hepatic and portal veins, and adjacent caudal vena cava are all visible in the liver of the normal cat and dog. Unlike plain radiography, which requires two views to complete the study, US

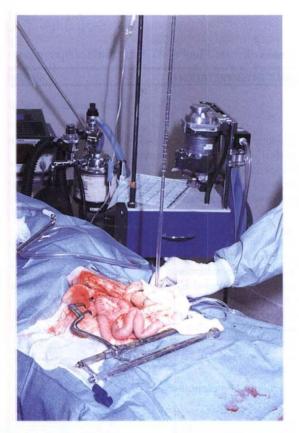


FIG 36-6

A 22-gauge intravenous catheter attached to an extension set, three-way stopcock, and water manometer has been placed in a mesenteric vein in preparation for intraoperative measurement of resting portal pressure. The catheter may also be secured in place and used for operative portal venography.

makes many slices through several planes to create a threedimensional reconstruction of the target structures.

Performing US and interpreting the recorded images are a blend of technical skill and experience. It is also important to remember that US is very sensitive to the presence of lesions but does not diagnose what the lesions are (i.e., it cannot yield a histological diagnosis). With a few exceptions, which predominantly involve lesions of the biliary tract and vessels, the ultrasonographic appearance of a variety of both benign and malignant hepatic lesions can appear very similar and histology of a liver biopsy is usually required for diagnosis. An animal should never be euthanized on the basis of an ultrasonographically identified "tumor" without histological confirmation because benign nodular hyperplasia or focal inflammatory lesions can look the same. Table 36-3 outlines the typical appearances of different hepatic lesions on ultrasonography.

Neoplasia may appear as hyperechoic or hypoechoic and focal or diffuse. Hepatic lymphoma often appears diffusely hypoechoic but can also appear hyperechoic. Some tumors, such as metastatic hemangiosarcomas, have a classically nodular hypoechoic appearance (Fig. 36-9).

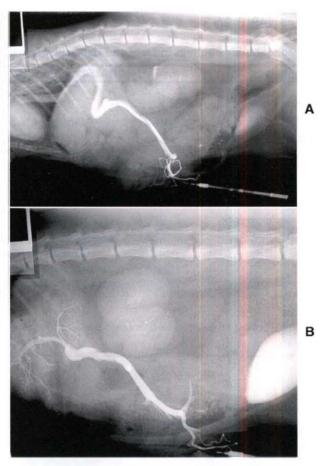


FIG 36-7

Operative mesenteric portal venography in a young domestic shorthaired cat before (A) and after (B) surgical correction (note improvement in hepatic portal blood flow in B with arborization of the contrast material within the small portal vessels in the liver). (Radiographs courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

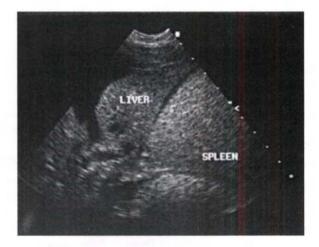


FIG 36-8

Abdominal ultrasound is enhanced by the presence of ascites. Ultrasound of the abdomen of a dog with chronic hepatitis and ascites. (Image courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)



TABLE 36-3

Ultrasonographic Findings in Dogs and Cats with Hepatobiliary Diseases

FINDING	POSSIBLE INTERPRETATIONS
Parenchyma Anechogenicity	
Focal	Cyst(s)—may be singular or multiple with septae; thin-walled Abscess(es)—may be poorly demarcated and have a heterogeneous echo pattern Hematoma(s)—appearance depends on maturity Lymphoma—may look like cyst if solitary
Hypoechogenicity	
Focal	Focal or multifocal neoplasia Regenerative nodule formation Extramedullary hematopoiesis Normal liver surrounded by hyperechoic liver Hematoma(s)
Diffuse	Abscess(es) or granuloma(s) Neoplastic or inflammatory cell infiltrates Passive congestion Hepatocellular necrosis Amyloid Extramedullary hematopoiesis
Hyperechogenicity	
Focal  Diffuse	Focal or multifocal neoplasia Nodular hyperplasia Mineralization (creates shadowing artifact) Fibrosis Gas (creates reverberation artifact) Hematoma or abscess Fatty infiltration (attenuates the sound beam) Lymphoma
	Fibrosis Neoplastic or inflammatory cell infiltrates Steroid hepatopathy (dogs only)
Tubular Structures—Biliary Tract	
Distended gallbladder Distended gallbladder and cystic duct Distended gallbladder and common bile duct Focal areas of gravity-dependent hyperechogenicity within biliary tract or gallbladder that cause acoustic shadowing Focal areas of hyperechogenicity within gallbladder that settle to dependent portion of gallbladder when animal's	Extrahepatic bile duct obstruction; persistent or recently relieved Severe cholangitis complex (cats) Choledochal cyst (rare) Normal (prolonged fasting) Cystic duct obstruction Extrahepatic bile duct obstruction; persistent or recently relieved Cholelithiasis "Sludged" or inspissated bile from severe cholestasis, prolonged anorexia, and dehydration
position changes Stellate or "kiwi fruit" appearance to gallbladder Intraluminal echoic masses in gallbladder Apparent thickened gallbladder wall	Gallbladder mucocele Neoplasia (polyp, malignant neoplasm) Adherent inspissated bile Cystic hyperplasia (focal) Cholecystitis, cholangitis Infectious canine hepatitis Hypoalbuminemia with edema formation Abdominal effusion Neoplasia



FINDING

**TABLE 36-3** 

Ultrasonographic Findings in Dogs and Cats with Hepatobiliary Diseases—cont'd

#### Tubular Structures - Blood Vessels

Dilated hepatic veins and portal veins

Prominent hepatic arteries

Distended portal vein with reduced velocity and flow Inapparent hepatic vessels

Inapparent portal veins

Aberrant vessel that communicates with systemic circulation Connection between a portal vein and an artery within one or more liver lobes

Many tortuous veins clustered around left kidney and along colon

#### **POSSIBLE INTERPRETATIONS**

Right-sided congestive heart failure

Pericardial disease

Intrathoracic caudal vena cava occlusion Hepatic vein occlusion (Budd-Chiari syndrome)

Reduced portal blood flow

Portal hypertension of any cause (by Doppler)

Cirrhosis

Severe fatty infiltration

Congenital portosystemic shunt

Portal vein thrombus

Intrahepatic portal vein hypoplasia

Intrahepatic or extrahepatic congenital portosystemic shunt

Arterioportal venous fistula

Acquired portosystemic shunts associated with portal hypertension



FIG 36-9

Ultrasonographic appearance of a hepatic hemangiosarcoma in a dog. Note the multiple hypoechoic nodules. (Image courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

Contrast-enhanced ultrasonography has recently been used to improve visualization of small hepatic metastases in dogs (O'Brien 2007). Typically, hepatic lipidosis in cats causes an increase in echogenicity and so does diffuse fibrosis such as cirrhosis in dogs. However, a cirrhotic liver may appear normal ultrasonographically.

Dilated anechoic (black) vascular channels and echoic bile ducts can be identified; biliary tract imaging is particularly useful in cats with suspected biliary tract disease (Fig. 36-10) or dogs and cats with suspected EBDO. The bile duct



FIG 36-10

Ultrasonographic appearance of dilated biliary tract in a cat with chronic cholangitis. (Image courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

can be followed ultrasonographically along its course toward the small intestine, and lesions in the pancreas or duodenum obstructing it can be identified.

A dilated gallbladder may indicate prolonged anorexia, unless dilated bile ducts, particularly the common bile duct, are also seen, which supports EBDO or chronic cholangitis/ cholangiohepatitis in cats (see Fig. 36-10). Intrahepatic or extrahepatic anomalous vessels may also be identified in animals with clinicopathologic evidence of severe chronic hepatobiliary disease or congenital PSS (Fig. 36-11). Congenital PSSs are typically single vessels, whereas acquired

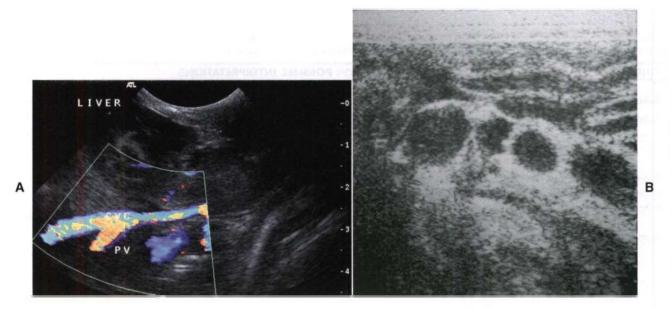


FIG 36-11

**A,** Doppler ultrasonographic findings of a congenital extrahepatic portocaval shunt in a young English Springer spaniel. **B,** Ultrasonographic appearance of multiple extrahepatic acquired portosystemic shunts in a 6-year-old German Shepherd Dog with noncirrhotic portal hypertension. *CVC*, Caudal vena cava; *PV*, portal vein. (Images courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

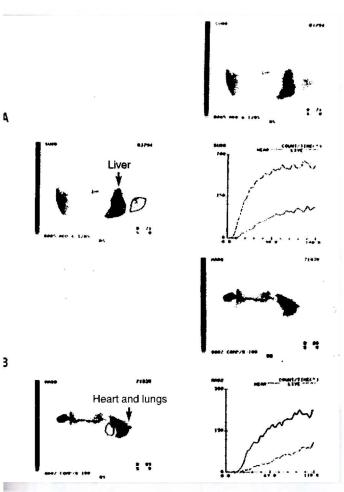
PSSs are usually multiple. Use of Doppler color-flow imaging confirms the location of the suspicious vessel(s) and the direction of blood flow within it. Doppler imaging can also provide supportive evidence of intrahepatic portal hypertension by allowing the assessment of the speed and direction of portal flow. Portal blood flow toward the liver (hepatopetal) is normal; away from the liver (hepatofugal) is abnormal. Whether the lesion is determined to be focal or diffuse, US can also be used as a guide to obtain diagnostic specimens for cytologic or histopathologic evaluation. US has developed into a valuable and critically important adjunct to diagnosis of hepatobiliary disease of cats and dogs by allowing characterization of structural changes not possible by any other modality and by providing a way to obtain needle liver biopsy specimens and bile duct samples in a visualized manner without the need for general anesthesia.

#### **SCINTIGRAPHY**

Other imaging modalities, such as scintigraphy (nuclear imaging), magnetic resonance imaging, contrast-enhanced harmonic ultrasound, and computed tomography, are available primarily through teaching or larger referral institutions. Of these imaging modalities, scintigraphy has been evaluated most thoroughly for diagnosis of hepatobiliary disease in cats and dogs. The isotope selected most often for clinical use is technetium-99m (99mTc), which is incorporated into the radiopharmaceutical specific for the planned study. For example, 99mTc bound to sulfur colloid, which is phagocytized by monocyte-macrophage cells of the liver and spleen, is given to assess liver mass. Images are made by col-

lection of emissions from decaying isotope using a gamma camera focused over the animal's liver region and recorded on radiographic film. The isotope has a short (6-hour) half-life; thus, although the animal must be relatively isolated for 24 to 48 hours and urinary and fecal waste stored until radioactivity has fallen to background levels, there is minimal radiation hazard to the animal or involved personnel. To distinguish medical from surgical causes of jaundice, <sup>99m</sup>Tc is combined with disofenin (Hepatolite). After an intravenous injection of radiopharmaceutical, scintigraphic images are made sequentially over 3 hours to determine whether the isotope has been taken up by the liver, excreted into the biliary tract, and expelled into the intestine. In cats and dogs with EBDO, no evidence of radiopharmaceutical is detected in the gallbladder or intestine.

Another application of scintigraphy is used in the diagnosis of PSS in cats and dogs. Following placement of pertechnetate labeled with <sup>99m</sup>Tc into the descending colon, the vascular path taken by the isotope after absorption is plotted. Time/activity curves determine whether the isotope arrived in the liver first, which is normal, or in the heart and lungs, which is compatible with any kind of portal venous bypass of the liver (Fig. 36-12). This approach has the advantage of specifically evaluating the portal blood supply rather than the hepatic mass, which may or may not be reduced in animals with congenital PSS or primary hepatobiliary disease and acquired PSS. The test results do not provide anatomic detail but only evidence of the presence or absence of congenital *or* acquired portosystemic shunting. Transcolonic portal scintigraphy is most helpful in confirming the



#### FIG 36-12

Transcolonic scintigraphy demonstrating the portal vascular path to the liver. **A,** Normal dog with isotope following a direct path to the liver and a small (5%) shunt fraction. **B,** Abnormal arrival of isotope in the heart and lungs of 1-year-old male Miniature Schnauzer with congenital portosystemic shunt and large (84%) shunt fraction. In each scan image the dog's head is to the right. (Courtesy Dr. Lisa J. Forrest, North Carolina State University, College of Veterinary Medicine.)

presence of a congenital PSS in a cat or dog with atypical clinicopathologic test results, equivocal abdominal ultrasound findings (e.g., normal-size liver, no identifiable vessel arising from the portal vein), and no evidence of portal hypertension (e.g., ascites).

#### LIVER BIOPSY

#### **General Considerations**

For many primary hepatobiliary diseases of cats and dogs, a hepatic biopsy is needed to establish a final diagnosis and prognosis. In some cases bile culture is also imperative. Biopsy is indicated to (1) explain abnormal results of hepatic status and/or function tests, especially if they persist for longer than 1 month; (2) explain hepatomegaly of unknown



#### BOX 36-2

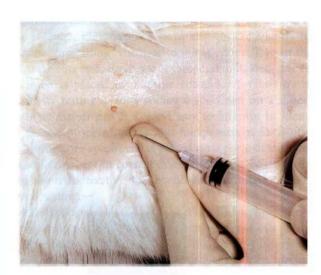
#### Patient and Operator Considerations for Hepatic Biopsy

#### **Patient**

- Characteristics of the suspected hepatobiliary disorder: liver size (small, normal, enlarged); texture (fibrotic or friable); focal, multifocal, or diffuse distribution; presence of abdominal effusion
- 2. Clinical stability and suitability for anesthesia
- 3. Coagulation status and platelet count

#### Operator

- 1. Available equipment
- 2. Experience with chosen technique
- 3. Complication rate for chosen technique
- 4. Size of specimen needed
- 5. Access to reliable veterinary pathology laboratory



#### FIG 36-13

A 4-year-old spayed female domestic short-haired cat with suspected hepatic lipidosis positioned in right lateral recumbency for blind fine-needle aspirate for cytology. With care taken to avoid the spleen, the needle is directed craniomedially into the liver.

cause; (3) determine hepatic involvement in systemic illness (although biopsy is not always necessary for this); (4) stage neoplastic disease; (5) objectively assess response to therapy; or (6) evaluate progress of previously diagnosed, not specifically treatable disease. Percutaneous hepatic biopsy is *not* performed if there is a good chance that the disease can be corrected surgically, such as in some cases of EBDO or congenital PSS; instead, a specimen is obtained at the time of surgery to complete the diagnostic evaluation. Several approaches are available; choice is dictated by patient and operator considerations (Box 36-2). In addition, in most cases of hepatic disease the accuracy of histological diagno-

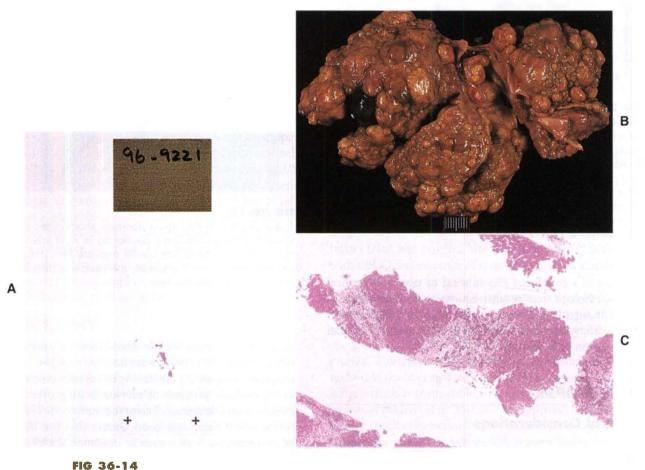
sis is better with larger (i.e., surgical or laparoscopic) rather than smaller (i.e., needle) biopsies.

All cats and dogs undergoing hepatic biopsy are fasted for at least 12 hours, regardless of the approach selected. In general, percutaneous needle core biopsy or aspiration (for cytologic analysis) of a single cavitary or solid lesion highly likely to be nonlymphoid cancer should be avoided unless the owner is unwilling to permit surgery for complete resection. Fine-needle aspiration of the liver for cytologic analysis is rarely advisable because of low diagnostic yield and often misleading results. The exceptions to this are for quick diagnosis of hepatic lipidosis in cats and possibly for suspected hepatic lymphoma, although even then the diagnosis may need to be confirmed histologically (Fig. 36-13). However, an overall correlation of only 30% in dog and 51% in cats was found in one study comparing the cytologic diagnosis with the histopathologic diagnosis of a variety of liver diseases (Wang et al., 2004).

In an especially small and/or firm fibrotic liver, it is difficult to obtain a biopsy specimen by percutaneous needle methods; small, fragmented specimens that are challenging

to interpret are often the result (Fig. 36-14). There is less than a 40% correlation between 18-gauge needle biopsy and wedge biopsy for certain hepatobiliary diseases (i.e., chronic hepatitis/cirrhosis, cholangitis, portovascular anomaly, fibrosis). If a needle technique is selected, the largest available instrument is used (preferably 14 gauge; minimum 16 gauge) and multiple samples are taken to ensure samples adequate for examination.

The animal's coagulation status is determined before a liver biopsy is performed, regardless of the approach. Ideally, a complete coagulation profile (one-stage prothrombin time [OSPT], APTT, fibrin degradation products, fibrinogen content, platelet count) is obtained; a platelet count and an activated clotting time or whole blood clotting time in a glass tube, as a screening test of the intrinsic coagulation cascade, are also acceptable. Bleeding after ultrasound-guided biopsy is more likely if the platelet count is less than 80,000 cells/µl or if the OSPT (dogs) or APTT (cats) is prolonged (Bigge et al., 2001). If possible, von Willebrand's factor is measured in susceptible breeds in advance of biopsy because results of standard coagulation tests are usually normal in affected



**A,** Liver specimen obtained percutaneously (with ultrasound guidance) from a dog with hepatic fibrosis and nodular regeneration (**B**). The specimen was difficult to obtain because the liver was firm and rubbery in texture. **C,** The resultant sample was difficult to interpret histologically.

dogs. A buccal mucosa bleeding time test provides indirect assessment of platelet function (see Chapter 87). In dogs with von Willebrand's disease, desmopressin acetate (DDAVP) is given (1  $\mu$ g/kg intranasal preparation subcutaneously) before surgery to enhance shift of von Willebrand's factor activity from endothelial cells to the plasma.

Mild abnormalities in coagulation test results do not preclude liver biopsy. In fact, results of routine coagulation tests may not correlate with liver bleeding times, as was found in one study of human patients. Liver biopsy should be delayed if there is clinical evidence of bleeding or marked abnormalities in results of coagulation tests. Because animals with complete EBDO may be vitamin K deficient (manifested by prolongation of both OSPT and APTT), treatment with vitamin K<sub>1</sub> (0.5 to 1.0 mg/kg [maximum of 10 mg] subcutaneously q12h for 3 treatments) is indicated for 1 or 2 days before surgery. Vitamin K supplementation can also improve coagulation times in animals with other liver disease, particularly cats. Repeating the OSPT and APTT within 24 hours after administration of vitamin K1 should demonstrate normal or near-normal values. If not, the dose can be adjusted and the procedure delayed. Although it may not seem rational to give vitamin K1 to animals with severe parenchymal hepatic disease before surgery, it has been of benefit to some animals and, if given properly, can do no harm. These animals may have high serum activity of proteins induced by vitamin K antagonism (PIVKA) that could impart bleeding tendencies. If there has been minimal improvement in coagulation test results after vitamin K1 has been administered, fresh frozen plasma is administered before biopsy. If bleeding is excessive during or after biopsy and cannot be controlled locally with direct pressure or application of clot-promoting substances, fresh whole blood or plasma is given (see Chapter 83 for transfusion guidelines).

## Techniques

Information gathered before biopsy must support the fact that the likelihood of acquiring a diagnostic sample without complications is high. A specimen procured from any area of the liver is considered representative of the disease. Because only a small stab incision large enough to accommodate the biopsy needle is needed (a No. 11 blade is the perfect choice for this purpose), healing in hypoalbuminemic animals is not compromised. If the operator is confident with the biopsy procedure, there is little time involved and only heavy sedation is required. If the results are nondiagnostic, a larger specimen is obtained for histopathologic examination, usually by laparoscopy or laparotomy.

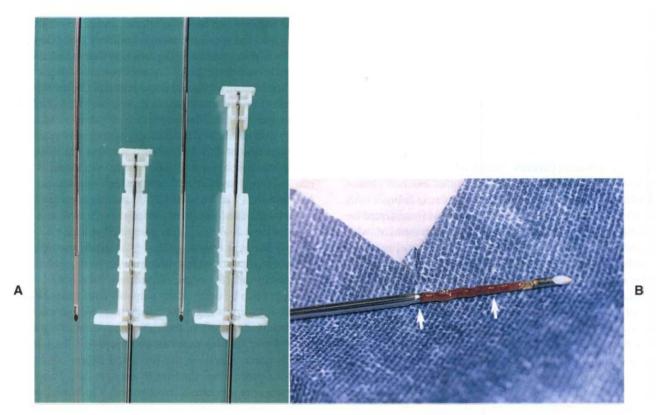
Biopsy can be performed blindly if the cat or dog has generalized hepatomegaly and the operator is confident of the path of the needle. The most common needle biopsy instruments are the Tru-Cut (Cardinal Health) and Jamshidi Menghini (Cardinal Health; Kormed Inc.) needles. The Jamshidi Menghini biopsy needles can be operated with one hand, and aspiration is used to sever and contain the specimen within the barrel of a 6- or 12-ml syringe. The Tru-Cut

needle requires two hands to operate and relies on the tissue falling into the specimen trough and then being severed by the sharp outer cannula (Fig. 36-15). One-handed operatable semi-automatic (e.g., Tenmo Evolution biopsy needle, Cardinal Health; VET-core biopsy needle, Global Veterinary Products Inc) and automatic (e.g., Pro-Mag Ultra Automatic biopsy instrument, Manan Medical Products; Bard Biopty biopsy instrument and Bard Biopty-Cut biopsy needle, Bard Inc) versions of this instrument are also available. These biopsy needles are intended for single use. Either the automatic biopsy instrument or the semi-automatic biopsy needle device can be used to obtain liver biopsies in dogs, but only the semi-automatic biopsy needle device should be used in cats. A recent study identified a high risk of fatal complications (i.e., unexpected fatal shock reaction) when an automatic biopsy instrument was used to obtain liver biopsies in cats (Proot and Rothuizen, 2006).

Biopsy can be done of any palpably enlarged lobe as long as care is taken to angle the needle to avoid puncturing the gallbladder. Most often, the animal is placed in right lateral recumbency for this purpose and biopsy of the left lateral lobe is done. Elevating the head and thorax slightly may assist in "presenting" the liver to the operator. Two or three complete core specimens are obtained; if indicated, one core specimen is placed in a sterile container for culture and sensitivity testing. Gently rolling a specimen on a slide for cytologic assessment is a good way to attempt to identify the disease process quickly and inexpensively. Each of the remaining core specimens is placed on a piece of stiff paper (e.g., filter paper) in correct orientation (Fig. 36-16) before immersion in fixative for histologic examination and/or special testing.

After biopsy, a small bandage is applied to keep the site clean during recovery, and the animal is placed in a position to allow body weight to compress the region of the biopsy sites in the liver (e.g., left lateral recumbency). Consideration should be given to postoperative analgesia; puncture of the liver capsule can be painful. The animal should be monitored carefully for any evidence of hemorrhage for several hours after the procedure. As long as the biopsy procedure proceeded smoothly and without unpleasant surprises (animal awake and struggling), only basic monitoring of mucous membrane color and the skin puncture site is needed. Naturally, if excessive hemorrhage or damage to other organs occurs with this blind technique, detection and treatment may be delayed.

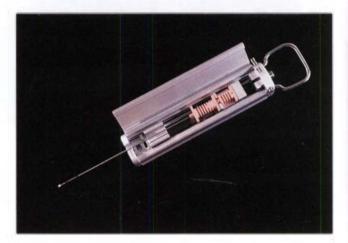
Visualized percutaneous needle biopsy, with the aid of either US (Fig. 36-17) or modified laparoscopic equipment (Fig. 36-18), allows selection of the site(s) and direct or indirect inspection after the biopsy. When the procedure is properly performed, serious complications are few. In an animal in which diffuse or multifocal hepatobiliary disease is suspected, multiple biopsy specimens are obtained safely. General anesthesia is usually required for use of a modified laparoscope. Aspiration of the gallbladder for cytologic analysis and culture can be accomplished with US guidance or by laparoscopy. Bile leakage may occur, even if a small-gauge



**FIG 36-15 A,** Tru-Cut biopsy needle with the specimen trough exposed (*left*) and then covered by the sharp outer cannula (*right*). **B,** Liver tissue filling the specimen trough (*between arrows*).



**FIG 36-16**Needle biopsy specimen affixed to a stiff piece of paper to preserve orientation of the sample during formalin fixation for histopathologic examination.



**FIG 36-17**Biopsy gun instrument with accompanying biopsy needle used for obtaining liver specimens with ultrasonographic guidance.

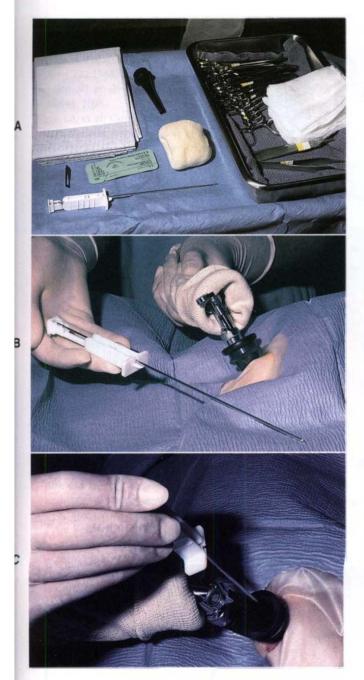


FIG 36-18
Modified laparoscopic approach for liver biopsy.

A, Readily available materials needed for the procedure.

B, A Tru-Cut biopsy needle is used for obtaining liver specimens. C, The liver is first inspected, and then the needle is passed through a sterile otoscope cone into the liver for tissue sampling. See Bunch et al. (1985) in Suggested Readings for further details on this procedure.

needle is used, so attempts are made to completely evacuate the gallbladder, and the needle should be placed in the gallbladder through the liver parenchyma to help prevent leakage. Some surgeons prefer to obtain bile during laparotomy when a purse-string suture can be applied to the aspiration site to prevent seepage. Large-volume abdominal effusion hinders direct inspection of the liver and associated structures and must be removed before laparoscopic biopsy is attempted.

An operative approach (laparoscopy [Fig. 36-19], laparotomy) is preferred for liver biopsy if the liver is small, US equipment is not available, or the operator is not experienced with the aforementioned percutaneous needle methods. Laparotomy is perfectly acceptable for dogs and cats that are good anesthetic risks and allows thorough examination of the liver, biliary tract, and portal vein as well as other abdominal structures, such as lymph nodes. Bile can be acquired easily and safely. The procedure is more prolonged, and healing complications may arise in severely hypoalbuminemic animals, notably those with intractable ascites, but larger samples for histopathologic examination and special staining techniques are obtainable (Fig. 36-20) and hemorrhage can be arrested directly. Use of nonabsorbable suture material and small cranial or flank incisions may lessen incision complications. Obviously, this is the approach of choice for surgically correctable diseases; a liver biopsy specimen is obtained concurrently.

As for the percutaneous biopsy techniques, liver and/or bile specimens for microbiologic culture are aseptically processed first. Impression smears for cytologic analysis are then made by gently touching the specimen to a slide before placing it in fixative. Excess blood is removed by blotting the sample on gauze before slides are made. Abnormal populations of cells (e.g., mast cells, lymphoblasts) are readily detectable using rapid stain systems such as Diff Quik (Harleco, Gibbstown, N.J.). For routine processing and histopathologic examination, liver tissue specimens are submerged in buffered 10% formalin at a ratio of at least 10 parts formalin to 1 part tissue. Samples for copper histochemical staining or tissue quantification are harvested and fixed or preserved according to the specifications of the pathology laboratory selected to do the assays. Other special stains for infectious agents or fibrous tissue, amyloid, glycogen, and other metabolic products are available, and their use is discussed with the attending pathologist before the tissue specimen is obtained. A portion of the specimen can be frozen for molecular studies (e.g., PCR for organisms or tumor clonality).

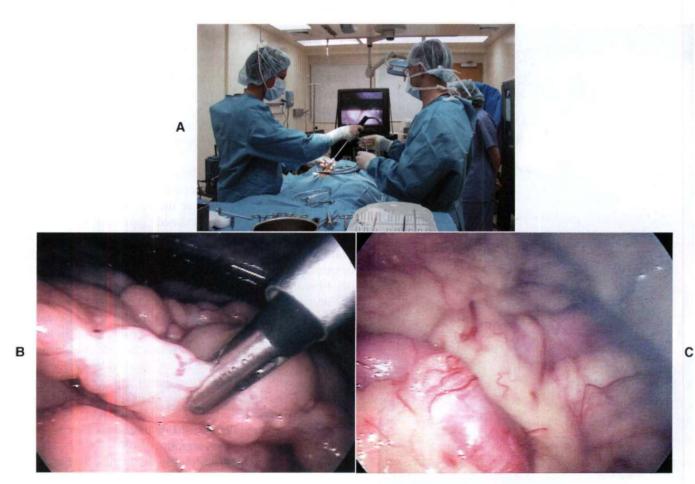


FIG 36-19

**A,** Laparoscopic liver biopsy. **B,** Tip of the biopsy instrument that is passed through one of the preplaced cannulas. **C,** Intraabdominal view of a dog with chronic hepatic disease and portal hypertension. Note the prominent, tortuous omental veins.

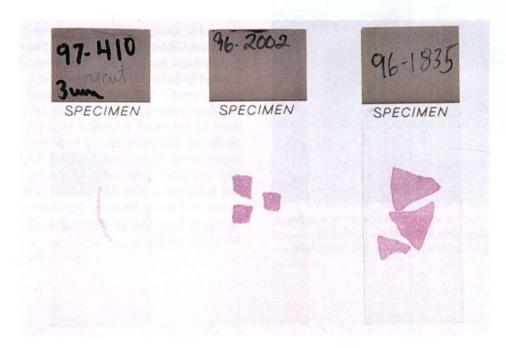


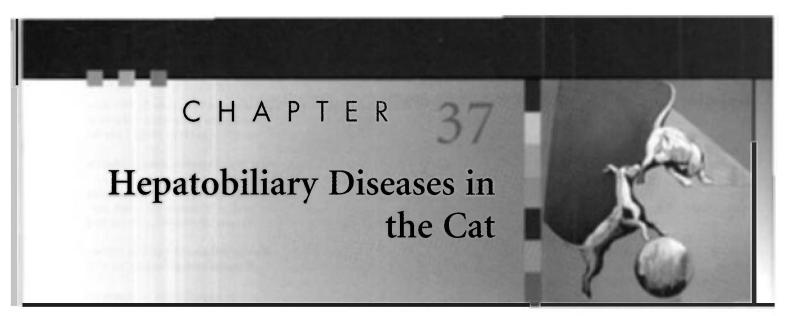
FIG 36-20

Comparison of liver specimens obtained by different methods and mounted on glass slides. These samples are adequate for histopathologic examination: percutaneous needle sample (*left*); samples obtained intraoperatively by use of an 8-mm skin biopsy punch (*middle*) or removal of a wedge specimen (*right*).

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## CHAPTER OUTLINE

GENERAL CONSIDERATIONS HEPATIC LIPIDOSIS

Primary Hepatic Lipidosis Secondary Hepatic Lipidosis BILIARY TRACT DISEASE

Cholangitis

Cholecystitis

**Biliary Cysts** 

EXTRAHÉPÁTIC BILE DUCT OBSTRUCTION

HEPATIC AMYLOIDOSIS

**NEOPLASIA** 

CONGENITAL PORTOSYSTEMIC SHUNTS

HEPATOBILIARY INFECTIONS

TOXIC HEPATOPATHY

HEPATOBILIARY INVOLVEMENT IN CATS WITH

SYSTEMIC DISEASE

## **GENERAL CONSIDERATIONS**

The causes, clinical signs, and prognosis of hepatobiliary tract diseases in cats are very different from those of dogs. Causes of liver disease in cats, both primary and secondary, are outlined in Table 37-1. Cats typically have hepatobiliary disease or acute hepatic lipidosis, but chronic parenchymal disease is uncommon in this species; in addition, feline liver disease rarely progresses to cirrhosis, as is sometimes the case in dogs. The clinical signs of hepatobiliary disease in cats are generally nonspecific and similar to the signs of inflammatory bowel disease (IBD) and pancreatitis; the three conditions may co-exist, further confusing diagnosis. Hepatic lipidosis presents with more classical signs of liver disease, including jaundice and encephalopathy. The important differences between feline and canine hepatobiliary diseases are outlined in Table 37-2 and Fig. 37-1.

The feline hepatopathies in this chapter are described approximately in order of their frequency in clinical practice in the United States. Historically, hepatic lipidosis has been most common in the United States and cholangitis most common in Europe, but lipidosis is becoming increasingly common in Europe, and cholangitis is now commonly recognized in the United States.

## HEPATIC LIPIDOSIS

## **Etiology and Pathogenesis**

Feline hepatic lipidosis may be primary or secondary to another disease, but in either case it is associated with a high mortality, unless the cat is intensively fed.

#### PRIMARY HEPATIC LIPIDOSIS

Primary or idiopathic hepatic lipidosis usually affects obese cats and remains the most common hepatic disease of cats in North America; it is also now emerging as an increasingly common problem in Europe. It is effectively an acute hepatopathy with a massive accumulation of fat in hepatocytes leading to acute loss of hepatocyte function, which is reversible if the fat can be mobilized (Fig. 37-2). The reason for the differences in prevalence in different countries is unknown but intriguing. Some researchers suggest environmental differences (e.g., differences in outdoor/indoor lifestyle or feeding habits), genetic differences among cats, or both.

The pathogenesis of primary hepatic lipidosis remains incompletely understood, but it seems to involve a combination of excessive peripheral lipid mobilization to the liver, deficiency of dietary proteins and other nutrients that would usually allow fat metabolism and transport out of the liver, and concurrent primary disturbances in appetite. Excessive mobilization of peripheral fat occurs particularly during periods of anorexia or stress in previously overweight cats. Concurrently, anorexia results in deficiencies of dietary proteins and other nutrients; cats are particularly susceptible to these because of their high dietary requirements (see Table 37-2). Some of these nutrients are important in fat metabolism and mobilization, particularly methionine, carnitine, and taurine, so deficiencies in these nutrients are implicated as contributing to the pathogenesis of the disease.



TABLE 37-1

## Clinically Relevant Hepatobiliary Diseases in Cats

PRIMARY	SECONDARY
Common	
Idiopathic lipidosis Neutrophilic cholangitis Lymphocytic cholangitis	Secondary lipidosis Hyperthyroidism Pancreatitis Diabetes mellitus
Uncommon or Rare	
Congenital portosystemic shunt Extrahepatic bile duct obstruction Liver flukes (except in hunting cats in endemic areas) Primary neoplasia Infections (see Box 37-5) Drug- or toxin-induced hepatopathy Biliary cysts Sclerosing cholangitis/biliary sclerosis Hepatic amyloidosis Intrahepatic arteriovenous fistula	Secondary neoplasia (less common than primary) Biliary stasis associated with extrahepatic sepsis Hepatic abscess

Methionine is an important precursor in the synthesis of an important hepatic antioxidant, glutathione, and hepatic concentrations of glutathione may decrease markedly in cats with hepatic lipidosis. Relative arginine deficiency will contribute to the resultant hepatic encephalopathy caused by decreased urea cycle activity. Concurrent primary appetite disturbances result in persistent and marked anorexia, which is likely due to disturbances in the complex neurohormonal control of appetite. Recent studies have suggested peripheral insulin resistance does not play a significant role in the disease.

### SECONDARY HEPATIC LIPIDOSIS

Secondary hepatic lipidosis is also common in cats; its pathogenesis is similar to the primary disease but complicated by the more marked neuroendocrine responses to stress. Secondary lipidosis can therefore be seen in cats that are less obese than those presenting with the primary disease and even in cats with normal or thin body condition. Any anorexic cat with concurrent disease must therefore be regarded as at high risk of hepatic lipidosis, and appropriate feeding support should be instituted as rapidly as possible. Secondary lipidosis may occur in association with any disease causing anorexia in cats but has been most commonly recognized in cats with pancreatitis, diabetes mellitus (DM), other hepatic disorders, IBD, and neoplasia.

#### **Clinical Features**

Most affected cats are middle-aged, but they can be of any age or sex. There is no reported breed predilection. Cats with

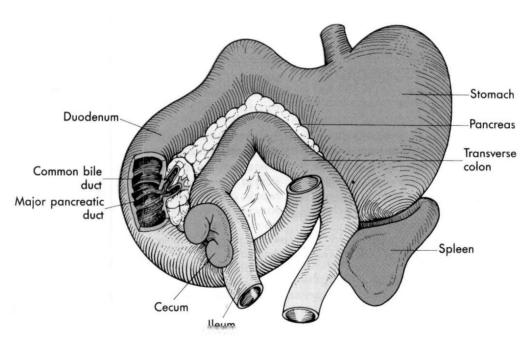


FIG 37-1
Anatomic relationship between pancreas, common bile duct, and duodenum in the cat. (From Strombeck DR: Small animal gastroenterology, Davis, Calif, 1979, Stonegate Publishing.)



TABLE 37-2

Important Differences Between Cats and Dogs with Hepatobiliary Disease

conjugated with taurine.

#### REASON FOR DIFFERENCE CATS **DOGS** Disease Cats have a higher prevalence Chronic parenchymal disease Unknown. of hepatobiliary diseases than is the most common, usually It has been proposed that the spectrum dogs. Chronic parenchymal progressing to fibrosis and high prevalence of biliary tract disease, fibrosis, cirrhosis, cirrhosis, with portal disease is due to differences in and portal hypertension are hypertension, Biliary tract anatomy, but this has not been much less common than in disease (acute and chronic) proved. In most cats the bile dogs. does occur but is duct joins the single major uncommon. Concurrent biliary tract disease, pancreatic duct before pancreatitis and inflammatory Secondary hepatic lipidosis entering the small intestine at can develop in association bowel disease are possible in major duodenal papilla, either species but are more with other diseases but this whereas in most dogs the bile common in the cat. Ascending is not usually a clinical duct enters the duodenum infections of the bile duct are problem. separately from two pancreatic also proposed to be more ducts (Fig. 37-1). common in cats. Underlying cause of hepatic Cats are particularly susceptible lipidosis in cats is not fully elucidated (see text) but likely to clinically serious hepatic due to differences in lipidosis (either primary or metabolism. secondary). Cats are less likely than dogs to Ability to Cats have a relative deficiency Because dogs are generally of glucuronyl transferase, more likely to scavenge, have toxic liver damage metabolize associated with environmental drugs/toxins reducing their ability to they may have more access metabolize drugs and toxins to hepatotoxins. Dogs toxins. However, cats are and making them more generally have no deficiency generally less able to susceptible to oxidant toxins. of enzymes, but there are metabolize toxins than dogs However, cats are more picky some breed variations (e.g., and are therefore more with their food and therefore Doberman Pinschers have an susceptible than dogs to toxic less likely to scavenge toxins. impaired ability to detoxify liver damage caused by many potentiated sulphonamides). potentially hepatotoxic drugs. Isoenzymes of Cats do not produce a steroid-Dogs have a steroid-induced Even mild increase in ALP in cats alkaline induced isoenzyme of alkaline isoenzyme of ALP and ALP implies significant ongoing phosphatase phosphatase (ALP) and the T12 has a long half-life: half-life problem. ALP does not (ALP) and increase with steroid therapy of ALP is very short in cats (6 of hepatobiliary ALP is 66 hours and glucocorticoid-(or HAC before development steroid hours). induced is 74 hours. hepatopathies Hyperadrenocorticism (HAC) is of diabetes mellitus) in cats. Hyperadrenocorticism is Steroid treatment and HAC are rare in cats. common in dogs. major differentials for high ALP in dogs. Hepatic Adapted to high-protein diet: Adapted to use dietary starch Cats will rapidly develop proteinmetabolism of postprandial hepatic and postprandial insulin calorie malnutrition and start glucose and gluconeogenesis from protein release results in glucose breaking down their own body protein and constantly high activity of storage. Can downregulate protein if fed a proteinprotein catabolizing enzymes restricted diet in liver disease. hepatic protein metabolizing in the liver, which cannot be Arginine deficiency can enzymes as necessary when downregulated. the diet is low in protein. contribute to the development High dietary requirement for Lower arginine requirement of hyperammonemia in cats arginine for the hepatic urea than cats. with liver disease if the cat is cycle. No obligate dietary taurine fed a diet deficient in arginine Taurine is an essential dietary requirement provided diet (such as dairy protein). requirement and bile salts all contains enough sulphur Taurine, arginine, and protein

amino acids.

deficiency can contribute to

the pathogenesis of hepatic

lipidosis in cats.

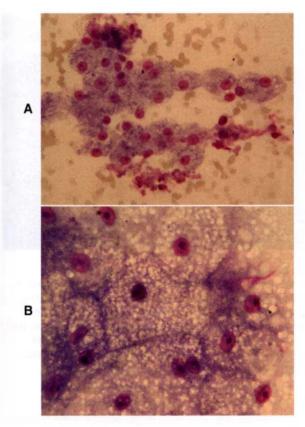


FIG 37-2
Cytology of (A) normal hepatocytes and (B) feline hepatocytes with hepatic lipidosis showing marked swelling of hepatocytes with lipid. (A and B, Courtesy Elizabeth Villiers; B, From Hall EJ, Simpson JW, Williams, DA, editors: BSAVA manual of canine and feline gastroenterology, ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

primary lipidosis are commonly obese, are housed indoors, and have experienced a stressful event (e.g., introduction of a new pet into the household, abrupt dietary change) or an illness that causes them to become anorexic and lose weight rapidly. The initiating event is not always known. Secondary lipidosis may affect cats of normal or thin body condition as well as obese animals, and the clinical signs are complicated by the signs of the concurrent disease. For example, the clinical signs of acute diabetic ketoacidosis are similar to those of developing hepatic lipidosis.

Clinical signs are typical of an acute (reversible) loss of hepatocyte function and of hepatocyte swelling with resultant intrahepatic cholestasis. Cats are usually jaundiced, and have intermittent vomiting and dehydration. They may also have diarrhea or constipation. There is usually palpable hepatomegally on physical examination. Hepatic encephalopathy, most often manifested as depression and ptyalism, is related to severe hepatocellular dysfunction and relative arginine deficiency, to which the anorexic cat is predisposed. Previously obese cats have extensive loss of muscle mass but maintain certain fat stores, such as those in the falciform ligament and inguinal region (Fig. 37-3).

## **Diagnosis**

The only truly definitive and reliable method of diagnosis and of identifying concurrent and causative conditions is histopathology of a wedge biopsy of liver obtained at laparotomy or laparoscopy or (less reliably) a Tru-Cut biopsy taken under ultrasound guidance. However, all of these procedures require a general anesthetic, and the majority of cats with hepatic lipidosis are too ill on presentation to be safely anesthetized. Therefore cytology of a fine needle aspirate (FNA) of the liver obtained either blindly or under ultrasonographic guidance in an awake or sedated cat can give a preliminary diagnosis; this will allow intensive management and tube feeding for a few days to stabilize the patient before anesthesia is considered for a more definitive diagnosis. Because coagulopathies are common in cats with lipidosis, a few days of therapy will help correct them before considering surgery. The clinician must be aware, however, that FNA cytology, although useful for emergency diagnosis and management, can be misleading in cats, and hepatic parenchymal disease can be misdiagnosed as lipidosis using this technique. In addition, concurrent diseases of the liver and other organs (including the pancreas and small intestine) will be overlooked without a laparoscopic or surgical biopsy. It is important to differentiate mild to moderate lipid accumulation in hepatocytes, which is common in sick and anorexic cats and causes no clinical problems, from clinically severe lipidosis on cytology (see Fig. 37-2).

FNAs can be taken under ultrasonographic guidance while the cat is being imaged or be obtained blindly if there is palpable hepatomegaly. The procedure is performed in a similar way to aspiration of a mass: The enlarged liver is palpated, and the abdominal wall overlying it is clipped and prepped. A 22-gauge needle is passed through the skin into the liver from ventrally on the left side, which prevents inadvertent puncturing of the gallbladder, and gentle suction is applied to a 5-ml syringe two or three times, before withdrawing and gently expressing the needle contents onto a slide (see Fig. 36-13). Analgesia is recommended for either procedure because puncture of the liver capsule is painful. Opiate partial agonists, such as buprenorphine, are a good choice; buprenorphine appears to be more effective than butorphanol as an analgesic in cats.

Clinically relevant hepatic lipidosis is usually easily recognizable on routine Giemsa or Diff-Quik staining of cytology samples or routine hematoxylin and eosin-stained histology samples (see Fig. 37-2). It is possible to use special staining procedures with Oil red O applied to snap-frozen biopsy samples to confirm that hepatocellular vacuolation is indeed lipid, but these procedures are not practical in a private practice setting. In addition, glycogen accumulation is uncommon in feline (as opposed to canine) hepatocytes.

Clinicopathologic findings reflect cholestasis and marked hepatocellular dysfunction. Hyperbilirubinemia is present in more than 95% of cases, and the activities of the hepatocellular enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are also markedly elevated in most cats. Alkaline phosphatase activity (ALP) is also markedly

elevated in more than 80% of cases; this is particularly relevant in cats, in which this enzyme has a short half-life and no steroid induction (see Table 37-2). In cats with classical primary (idiopathic) lipidosis, a particular hallmark of the disease is an inappropriately low γ-glutamyl transferase (GGT) activity, which is only mildly increased in the face of marked increase in the activity/concentration of the other cholestatic markers (i.e., bilirubin and ALP). This is in contrast to cats with primary biliary tract disease in which both GGT and ALP activities are high. However, in cats with secondary lipidosis associated with an underlying primary hepatopathy or pancreatic disease, GGT activity may be high as well. Therefore finding a high GGT activity does not rule out hepatic lipidosis but should stimulate a search for an underlying cause. Blood urea (BUN) concentration is low in more than half of the cats with lipidosis, reflecting generalized hepatocyte dysfunction. Electrolyte abnormalities are relatively common and can contribute to mortality if not addressed. Up to a third of cats are hypokalemic, and hypophosphatemia has been reported in 17% of the cases; hypomagnesemia has also been reported in cats with lipidosis. Hypokalemia was a poor prognostic indicator in one study (Center et al., 1993). There is no value in measuring serum bile acids as an indication of hepatic function in these cats because they will be high as a result of the concurrent cholestasis. Fasting cholesterol and glucose concentrations may also be high, and sometimes hyperglycemia is so marked as to result in glucosuria. This is usually a stress/metabolic response and typically resolves after appropriate therapy. However, some cats may become diabetic as a result of an underlying disease process, or DM may be the cause of their lipidosis; therefore blood and urine glucose and ketones should be monitored carefully. The appearance of ketonuria in addition to glycosuria in a hyperglycemic cat is highly suggestive of overt DM.

Hemostatic abnormalities are common in cats with lipidosis, occurring in between 20% and 60% of the cases. They are more reliably detected with the PIVKA test (proteins invoked by vitamin K absence; Center et al., 2000), but PIVKA tests are not readily available to many practitioners, and overt prolongation of clotting times are also seen in some cases. Anemia is present in about a quarter of cats, and there is often an increase in Heinz bodies. Because lipidosis is non-inflammatory, a neutrophilia is not characteristic but may occur as a result of another underlying disease.

Radiographs show hepatomegaly in most cases, whereas abdominal effusion is uncommon (Fig. 37-3). Ultrasonography helps differentiate parenchymal from biliary tract disease and also allows assessment of other abdominal organs to look for underlying disease, particularly of the pancreas and intestine. Characteristically, the lipidotic liver appears hyperechoic, although this is not a specific finding and can also be seen in cats with other generalized parenchymal diseases, such as lymphoma or hepatic amyloidosis.

Additional diagnostic tests are performed to determine the presence of concurrent illnesses that could be causing protracted anorexia and secondary hepatic lipidosis. Tests

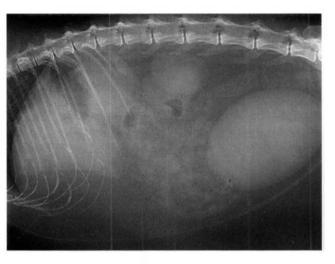


FIG 37-3
Lateral abdominal radiograph of a Domestic Short-haired cat with hepatic lipidosis secondary to prolonged fasting because of a diet change. Note maintenance of large falciform fat pad below the liver in spite of weight loss and loss of subcutaneous fat under the spine. (Courtesy the diagnostic imaging department at the Queen's Veterinary School Hospital, University of Cambridge.)

are selected according to clues in the history, physical examination, and clinicopathologic and ultrasonographic evaluations. For example, serum feline specific pancreatic lipase immunoreactivity should be evaluated in cats suspected of having pancreatitis (see Chapter 40).

### **Treatment and Prognosis**

Treatment recommendations for cats with hepatic lipidosis are outlined in Box 37-1. The single most important factor in reducing mortality is early and intensive feeding of a highprotein diet. In most cases, this requires some form of tube feeding. If the cat is very ill at presentation, a nasoesophageal tube can be placed for the first few days while the cat is stabilized (Box 37-2 and Fig. 37-4) and then an esophagostomy or gastrostomy tube may be placed for long-term feeding (see Box 37-2 and Fig. 37-5). Most cats need 4 to 6 weeks of tube feeding, but many cats can be sent home with a gastrostomy tube in place for home feeding once they have stabilized. A high-protein diet, such as those manufactured for feline intensive care patients, is ideal (e.g., Royal Canin feline concentration instant or Hills AD diet or "Fortol" liquid feed [Arnolds]). In some cats, however, a high-protein diet will worsen signs of encephalopathy during the first few days of therapy. Attempts should be made to control this by other methods, such as by feeding smaller amounts more frequently rather than by reducing the protein content of the diet. Concurrent pancreatitis does not alter the dietary recommendations; the current recommendations in cats with pancreatitis is to feed them as soon as possible and not to restrict fat (see Chapter 40).

Fluid and electrolyte abnormalities should also be addressed effectively in the first few days, and antiemetics



## BOX 37-1

#### Outline of Treatment of Hepatic Lipidosis in Cats

- Treat any identifiable underlying cause as effectively as possible, but also concurrently start other treatment: Do not rely on treating the cause alone to resolve the disease in secondary cases; in most cases the anorexia will persist unless active measures are taken to feed the cat.
- Institute fluid therapy and nutritional support as soon as possible.
  - Fluid therapy: Intravenous fluid support is necessary in the early stages of therapy (maintenance rates + replacement for any fluid lost, e.g., in vomiting). Measure and replace any electrolyte deficits, particularly potassium and phosphate. Carefully monitor blood glucose and electrolytes, particularly potassium and phosphate, which may become low during treatment. Normal saline with added potassium chloride as necessary is the most useful fluid. Dextrose is avoided because it may worsen hyperalycaemia and lactated Ringer's may be contraindicated with marked hepatocellular dysfunction because the lactate may not be metabolized to bicarbonate. There is NO evidence that adding insulin to the fluids helps; in fact, it increases the risk of serious hypokalaemia and hypophosphatemia. After the first few days, fluid and electrolyte needs can be supplied via the feeding tube.
  - Nutritional support should be instituted as soon as possible. A nasoesophageal tube can be used for temporary support for the first few days before general anesthetic for more permanent tube placement. A gastrostomy or esophagostomy tube will usually be required long term because feeding will be necessary in most cases for 4 to 6 weeks. A diet that is as high in protein as possible should be given, preferably managing any resultant encephalopathy by other means such as feeding little and often. This means using a diet manufactured for nutritional support of hypermetabolic sick cats if possible. A diet such as Royal-Canin concentration instant diet or Hill's AD would be suitable. Some clinicians add extra nutrients

- such as taurine, arginine, B vitamins, or carnitine to the tube feed, but there is no firm evidence that any of these are necessary if a balanced feline diet is used.
- Amount to feed: start conservatively with the resting energy requirement (RER) because cats have had prolonged anorexia and complications of feeding are more common in the first few days. Start with small amounts frequently (or even slow-rate constant infusion) and gradually build up to higher volumes and lower frequency over the first week. The calorie intake can then be gradually increased to the metabolic energy requirement (MER).

$$RER = 50 \times BW$$

$$MER = 70 \times BW$$

- Appetite stimulants are not recommended because they are of very limited efficacy and potentially hepatotoxic.
- Additional vitamins are necessary in some cats: cobalamin (vitamin B<sub>12</sub>) may be deficient, particularly in cats with concurrent pancreatic and/or ileal disease (see Chapter 40) and should then be supplemented parenterally. Vitamin K-responsive coagulopathies are very common in cats with lipidosis, and some authors recommend supplementation in all cats at the start of treatment with 0.5 mg/kg given intramuscularly q12h for three doses.
- Antiemetics and promotility agents such as ranitidine (2 mg/kg PO or IV twice a day) and metoclopramide (0.5 mg/kg IM or PO q8h or 1 to 2 mg/kg q24h IV as a slow infusion) may be necessary if the cat is vomiting or has delayed gastric empting with reflux of food up the feeding tube.
- Antioxidants are also recommended, particularly S-adenosylmethionine (20 mg/kg or 200 mg total once a day) on the basis of some limited but supportive evidence in cats. There is currently no evidence in support of the use of ursodeoyxcholic acid in cats with lipidosis.

should be used if necessary. Many cats require vitamin K therapy for coagulopathies [0.5 mg/kg of vitamin K1 (Phytomenadione) subcutaneously or intramuscularly q12h for 3 days]; clinicians should not place any central catheters or invasive feeding tubes until hemostasis is normal. There is the potential for serious and undetected bleeding around a central venous catheter in a cat with a coagulopathy. Antioxidant therapy is also indicated in cats with lipidosis because of the associated glutathione depletion in many cats; vitamin E and S-adenosylmethionie supplementation should be considered. (S-adenosylmethionine: 20 mg/kg once a day given whole on an empty stomach, cats and dogs, or 100- to 400-mg total dose daily in cats. The ideal dose of vitamin E in a cat is unclear, but the authors use 100 IU daily.)

Prognosis for recovery in cats with hepatic lipidosis is reasonably good as long as feeding is rapidly and effectively instituted. Studies have reported between 55% and 80% survival in intensively fed cats, whereas mortality is very high without supportive feeding. One large study (Center et al., 1993) suggested that anemia, hypokalemia, and older age were poor prognostic indicators for survival and that cats with secondary hepatic lipidosis may do slightly worse than those with primary disease. However, the differences were not significant, which suggests that it is well worth treating cats with secondary lipidosis as aggressively as those with primary disease.

## **BILIARY TRACT DISEASE**

Biliary tract diseases are the second most common disorders of the feline liver (see Table 37-1). This contrasts with dogs,



BOX 3*7*-2

## Outline of Method of Placement of Feeding Tubes

#### Nasoesophageal Tube

For short-term nutritional support (<1 week) while stabilizing cat before placement of esophagostomy or gastrostomy tube.

#### Placement

- Premeasure tube to allow placement in caudal esophagus, not stomach; this minimizes gastric reflux. Premeasure to seventh intercostal (IC) space from nose or 75% of distance from nose to last rib if animal is so obese that ribs cannot be counted. (Orogastric: ninth IC space or 90% of distance nose to last rib.) Mark tube with pen or piece of tape.
- Apply local anesthetic to nose. Mild sedation may also be necessary, preferably with buprenorphine or butorphanol, but often not.
- Lubricate tube and advance into ventral meatus; it is important not to advance into middle or dorsal meatus or stops at the ethmoturbinates. It may be helpful to raise cat's head slightly to do this.
- Hold cat's head normally as you approach pharynx to prevent tracheal intubation. Allow cat to swallow, and advance tube to measured mark or tape.
- 5. To check that the tube is correctly positioned, instill water and then air and auscultate over left flank for bubbling in stomach. If still uncertain, perform a radiograph. If tube does not have a radiodense line, inject some ionic contrast material into tube first.
- Pass tube over top of cat's head, and suture or glue tapes at level of nares and top of head; be careful to avoid interfering with cat's whiskers.
- 7. Put on elizabethan collar.
- 8. Flush regularly with warm water before and after feeds.

#### **Gastrostomy Tube**

Indicated for longer-term nutritional support (>1-2 weeks). The tube must be in at least 5 to 7 days for surgical tubes and 14 to 21 days for endoscopically placed tubes to allow adhesions to form between stomach and body wall.

Advantages over nasoesophageal tube of longer-term support: can feed thicker food; better tolerated by animal, which is more likely to start eating with tube in place; easier to manage; could be managed by owner at home. However, it is necessary to use a general anaesthetic for placement.

## Placement at laparotomy

Placement is usually via a left paracostal laparotomy but can be via midline laparotomy.

- Pull stomach to body wall and exteriorize. Pack off area between stomach and body wall.
- Lay two concentric purse-string sutures in greater curvature of body or fundus of stomach, and incise in center of these
- Insert feeding tube or catheter; it is best to use a Pezzar mushroom-tipped catheter and not a foley because the latter show a propensity to disintegrate too early.
- Tighten purse strings; they should be tight enough to seal but not so tight that they cause necrosis of gastric wall.

- Suture stomach to abdominal wall using simple interrupted pattern; you may wrap omentum around tube between stomach and body wall.
- Exit catheter through separate stab incision, and secure to skin.
- 7. Plug to stop air from filling stomach and food from leaking out, and cover with a dressing/body bandage. Put on an elizabethan collar.
- 8. Clean stoma regularly, and flush tube regularly with warm water, even when not in use.

#### Placement endoscopically

This is quicker and less invasive if you are not already doing a laparotomy, but it is necessary to use a fiberoptic endoscope. (However, it is possible to use gastrostomy introducers and do it blind, although there is a higher incidence of traumatic injuries with inexperienced operators, who can easily push the tube through visceral surface of stomach and damage or entrap the spleen. It is best to insufflate stomach first if doing it blind and attempt it only if taught by an experienced operator and practiced on cadavers first.) Several companies make PEG tube kits suitable for veterinary use.

- Clip and aseptically prepare an area of skin caudal to left costal arch.
- Pass endoscope through mouth into stomach and inflate stomach.
- Insert catheter into stomach through stab incision in shaved area of body wall.
- 4. Remove stylet, and pass thick nylon suture through
- Grab suture with biopsy instrument of endoscope, and pull it out of mouth.
- Attach suture to feeding tube as directed by manufacturer.
- Pull the whole assembly back into the stomach by gentle traction on the nylon where it exits the body wall.
- Pull the feeding tube out through the body wall, and secure it with a second stent outside and sutures.
- Cap and cover as directed by manufacturer, and place an elizabethan collar to prevent interference.
- Clean stoma regularly, and flush tube regularly with warm water, even when not in use.

Note on gastrostomy tube removal: Do not remove for at least 5 to 7 days (surgical) or 14 to 21 days (PEG tubes). Method of removal depends on tube placed. Always refer to the manufacturer's instructions, and do not attempt simply to pull the tube out. Most manufactured tube kits for human use cannot be pulled out but have to be cut close to the body wall and the end retrieved from the stomach endoscopically. (The end can be left to pass through into the feces in medium-to large-breed dogs but not cats, in which it may act as a pyloric foreign body.) The Pezzar mushroom-tipped catheters placed surgically can be removed completely by using a stylet in the tube to flatten out the mushroom.

Experience with a trained operator is highly recommended before attempting surgical placement of a gastrostomy tube or blind placement of a gastrostomy tube.

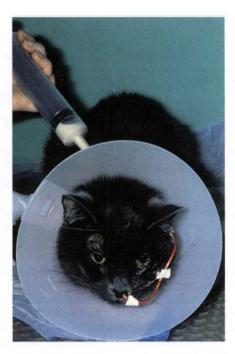


FIG 37-4
Nasoesophageal tube in place in a cat being fed a liquid enteral diet



FIG 37-5
Cat with gastrostomy tube to permit long-term feeding.

in which parenchymal diseases are most common. As discussed in the previous section, cats also often have concurrent pancreatitis and/or intestinal disease; it has been proposed that this is a reflection of the anatomy of their pancreatic and bile ducts, which usually join before entering the proximal duodenum through a common outflow tract (see Fig. 37-1). It has been proposed that this increases the likelihood of intestinal contents being refluxed up both the pancreatic and bile ducts during vomiting. However, it is also possible that the disease associations reflect common causative agents or events independent of the anatomy in this species.

The nomenclature of biliary tract disease has recently been standardized by the World Small Animal Veterinary Association (WSAVA); its recommended categorizations of disease will be used here (Rothuizen et al., 2006; Table 37-3). A wide variety of alternative names have been used in the literature, sometimes blurring the categories and confusing comparisons between studies. It is to be hoped that a standardized nomenclature will aid in the search for causes and treatment of these diseases.

All disorders of the biliary tract in cats can present with very similar clinical signs, including lethargy, anorexia, and jaundice. Clinical, clinicopathologic, and diagnostic imaging findings do not allow differentiation of the types of disease; in most cases, cytology, culture of bile, and histopathology of the liver are necessary for accurate diagnosis and most effective treatment.

#### CHOLANGITIS

Cholangitis refers to inflammation of the biliary tract, which in some (but not all) cats may also extend to the surrounding hepatic parenchyma. It is more common in cats than in dogs, and it is typically divided into three categories, likely associated with different etiologies: neutrophilic cholangitis, lymphocytic cholangitis, and chronic cholangitis associated with liver fluke infestation.

## **Neutrophilic Cholangitis**

Neutrophilic cholangitis is also known as suppurative cholangitis, exudative cholangitis/cholangiohepatitis, and acute cholangitis/cholangiohepatitis.

## **Pathogenesis and Etiology**

This process is believed to be due to an ascending bacterial infection originating in the small intestine. The most common organism isolated is Escherichia coli, although Streptococcus spp., Clostridium spp., and even occasionally Salmonella spp. may be involved. Concurrent pancreatic and intestinal disease are common (as outlined in the preceding sections). The result is a neutrophilic infiltrate in the lumen of the bile duct and often also invasion of the bile duct walls with neutrophils and edema and neutrophils within the portal areas (Fig. 37-6). Occasionally, an associated hepatic abscess may develop. Cholecystitis (inflammation of the gallbladder) may occur concurrently, or the two conditions may occur separately. A more chronic stage of neutrophilic cholangitis is also recognized; in these cases there is a mixed inflammatory infiltrate in the portal areas consisting of neutrophils, lymphocytes, and plasma cells. These cases are thought to represent more chronic, persistent infection of the biliary tract, but there is some overlap with cats with lymphocytic cholangitis according to some studies.

#### **Clinical Features**

Cats of all ages and breeds can be affected, but acute cholangitis is most often seen in young to middle-aged cats. It usually presents acutely (less than a month's history), although the more chronic form may be present for longer.



TABLE 37-3

Outline of Currently Recommended WSAVA Classification of Feline Biliary Tract Disease

NAME OF DISEASE	OLD NAMES PREVIOUSLY USED IN THE LITERATURE	CAUSE OF DISEASE	FINDINGS ON LIVER PATHOLOGY	RECOMMENDED DIAGNOSTIC PROCEDURES
Neutrophilic cholangitis	Suppurative or exudative cholangitis/ cholangiohepatitis Chronic phase: some previously reported cases of "lymphocytic" or "chronic" cholangiohepatitis would now fall into this category.	Likely ascending bacterial infection from small intestine	Acute phase: neutrophils in lumen and/or epithelium of bile ducts. May also be edema and neutrophils in periportal area, parenchyma, and occasionally hepatic abscess.  Chronic phase: mixed inflammatory infiltrate in portal areas, including neutrophils, lymphocytes, plasma cells, and sometimes some fibrosis and bile duct proliferation	Cytology and culture of bile aspirates are necessary for diagnosis. Ultrasound and histopathology can be suggestive but are not obligatory, and changes may be absent on either of these.
Lymphocytic cholangitis	Lymphocytic cholangiohepatitis; lymphocytic portal hepatitis; chronic cholangiohepatitis; nonsuppurative cholangitis: but note overlap of these definitions with the chronic phase of neutrophilic cholangitis	Unknown — may be immune- mediated disease	Infiltration of small lymphocytes into the portal regions. Variable portal fibrosis and bile duct proliferation. Lymphocytes may also be present within biliary epithelium. Occasional plasma cells and eosinophils may be seen. Difficult to differentiate some cases from well-differentiated lymphoma.	Liver histopathology is necessary for diagnosis. Changes may be found on ultrasound and bile cytology but will not give a definitive diagnosis.
Chronic cholangitis associated with liver fluke		Liver fluke	Dilated larger bile ducts with papillary projections and marked periductal and portal fibrosis. Slight to moderate inflammation of portal areas and ducts with neutrophils and macrophages and limited numbers of eosinophils. Flukes and eggs may be seen in ducts.	Ultrasonography of dilated bile ducts + history of possible exposure + demonstration of fluke eggs in feces or bile aspirates (see text). Histopathology supportive.

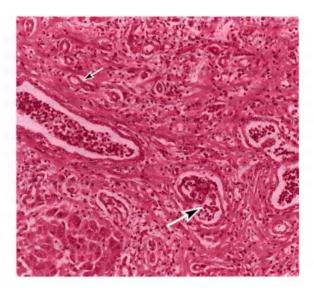
Data from Rothuizen J et al: WSAVA standards for clinical and histological diagnosis of canine and feline liver diseases, Oxford, UK, 2006, Saunders Ltd, Elsevier.

Cats typically have signs of biliary stasis and sepsis with lethargy, pyrexia, and jaundice.

## Diagnosis

Clinicopathologic and imaging findings show overlap with the other diseases of the biliary tract, so a definitive diagnosis of neutrophilic cholangitis cannot be made simply from a characteristic history and clinicopathologic findings. However, cats with this acute disease tend to have higher segmented and band neutrophil counts, ALT activities, and total bilirubin concentrations than cats with lymphocytic cholangitis. They may have a coarse or nodular texture to the liver on ultrasonography and may develop dilated biliary tracts more chronically, but cats with the truly acute disease may have no dilation of the biliary tract on ultrasonography.

An accurate diagnosis of neutrophilic cholangitis caused by acute ascending infection requires cytology and culture of bile. Histopathology of the liver alone is not enough in this particular disease because in many cases the disease is confined to the biliary tract, and changes on liver pathology are mild and nonspecific, Samples of bile for bacterial culture can be taken carefully from the gallbladder during laparotomy or laparoscopy or under ultrasonographic guidance. There is a small but definite risk of bile leakage, particularly if the gallbladder wall is devitalized and/or there is increased pressure within it. In these cases it might be safer to obtain a sample at laparotomy rather than under ultrasonographic guidance. In the latter case a general anesthetic is strongly recommended to prevent patient movement while the needle is in the gallbladder, which greatly increases the risk of bile leakage. The needle should be placed in the gallbladder



Photomicrograph of liver specimen from a cat with neutrophilic cholangitis. Notice the neutrophilic inflammation in and around bile ducts (large arrow). Biliary ductular hyperplasia is also present (small arrow) (hematoxylin-eosin stain).

through the hepatic parenchyma further to reduce the risk of leakage. The cat should be monitored carefully for any leakage of bile after the procedure; any suspicion of leakage and bile peritonitis warrants surgery. Cytology of bile usually shows bacteria and neutrophils, and culture and sensitivity tests should be performed.

## **Treatment and Prognosis**

Cats should be treated for 4 to 6 weeks with an appropriate antibiotic on the basis of the results of culture and sensitivity tests. Amoxycillin is a good initial choice at a dose of 15-20 mg/kg, PO q8h. Ursodeoxycholic acid may be given as an additional choleretic and antiinflammatory agent at a dose of 15 mg/kg, PO q24h, although there are no studies demonstrating their benefit in cats. Septic or extremely sick cats may require hospitalization for intravenous (IV) fluid and IV antibiotic administration during the initial stages of therapy. Careful attention should be paid to feeding anorexic cats to prevent the concurrent development of hepatic lipidosis; a high-protein diet designed for critical care use, as outlined in the lipidosis section, would be much more appropriate in these animals than a protein-restricted liver diet. The prognosis is generally good, and these cats usually recover completely provided they are treated early and appropriately. It is thought that the more chronic form of neutrophilic cholangitis may represent long-term persistence of a lowgrade infection in untreated or only partially treated cats.

### Lymphocytic Cholangitis

Lymphocytic cholangitis is also known as *lymphocytic cholangiohepatitis*, *lymphocytic portal hepatitis*, and *nonsuppurative cholangitis*.

## Pathogenesis and Etiology

Lymphocytic cholangitis is a slowly progressive chronic disease characterized by infiltration of the portal areas of the liver with small lymphocytes. Occasionally, plasma cells and eosinophils may also be seen. There is often associated proliferation of bile ducts, and there may be portal fibrosis. It particularly affects the larger bile ducts, which may become irregularly distended with thickened walls but usually remain patent. In severe cases the main differential diagnosis on histology is lymphoma. The cause is unknown. An immunemediated etiology has been suggested by some researchers, but the disease does not resolve with immunosuppressive medication. Other studies have suggested possible infectious etiologies, such as Helicobacter spp. or Bartonella spp. (Boomkens et al., 2004; Greiter-Wilke et al., 2006; Kordick et al., 1999), although more evidence is required before infectious organisms are confirmed as a cause. However, the use of immunosuppressive medication in these cases is subject to question.

#### **Clinical Features**

Cats with lymphocytic cholangitis are typically young to middle-aged, and Persians appear to be overrepresented. They tend to have a long history (months to years) of waxing and waning low-grade illness. Many become jaundiced, and they often lose weight and have intermittent anorexia and lethargy, but they are less likely to be pyrexic than cats with neutrophilic cholangitis. About a third of cats may also present with a high-protein ascites, reportedly most commonly in the United Kingdom. This makes differentiation from feline infectious peritonitis (FIP) important. Ultimately, the differentiation in these cats can be made only on histopathology.

## **Diagnosis**

Diagnosis in these cases relies ultimately on hepatic histopathology, although ultrasonographic and clincopathologic findings can support a presumptive clinical diagnosis. Increases in liver enzyme activities are mild to moderate and tend to be less marked than in cats with neutrophilic cholangitis. Peripheral blood neutrophilia is less common than in cats with the acute disease but may be present. A particular feature of most cats with lymphocytic cholangitis is an increase in r-globulin concentration, which again may cause confusion with FIP. Radiographic signs are nonspecific: There may be hepatomegaly (which is often due to enlargement of the larger bile ducts) and in some cases ascites (Fig. 37-7). Ultrasonography is more helpful and reveals dilation of the biliary tract in all cases (see Fig. 36-10). The common bile duct typically appears dilated, and there may be dilation of the gallbladder and "sludge" within it. The main differential diagnosis for these cats is extrahepatic biliary obstruction; the ultrasonographer should attempt to rule this out by carefully imaging the surrounding pancreas, small intestine, and mesentery.

It is very important to evaluate a hemostasis profile before performing a liver biopsy in view of how commonly coagulation times are prolonged in cats with liver disease. Vitamin

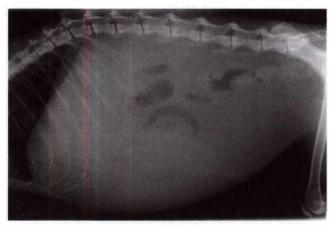


FIG 37-7
A lateral abdominal radiograph from a cat with lymphocytic cholangitis and associated ascites. The major differential diagnosis in this case would be feline infectious peritonitis. (Courtesy the diagnostic imaging department, The Queen's Veterinary School Hospital, University of Cambridge.)

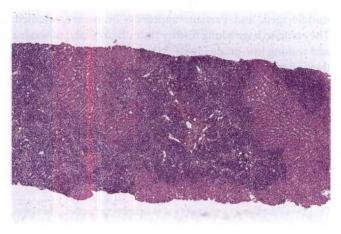


FIG 37-8
Photomicrograph of liver specimen from a cat with severe lymphocytic cholangitis. There is intense mononuclear cell infiltration in the portal tract (center).

K should be given before biopsy (0.5 mg/kg of vitamin K1 SQ or IM q12h for 3 days) if there is any concern about clotting function; fresh frozen plasma should be available to manage postbiopsy bleeding if it occurs. Bile aspiration is not necessary unless the disease is more acute and there is a possibility of neutrophilic cholangitis. Histology is important to rule out FIP (see Chapter 97). The typical hepatic lesion in cats with FIP is a multifocal pyogranulomatous reaction with evidence of vasculitis or perivasculitis, which is quite distinct from the periportal lymphocytic infiltrate seen in cats with lymphocytic cholangitis (Fig. 37-8). Serology or PCR for *Bartonella* spp. might be considered, although the importance of this organism in the naturally occurring disease is unclear.

## **Treatment and Prognosis**

Researchers disagree on the recommended therapy of this disease, which likely reflects our uncertainty about the etiology. A number of authors recommend immunosuppressive doses of corticosteroids. However, although these tend to ameliorate the acute flare-ups of the disease, they do not lead to resolution of signs, and the condition invariably recurs. Antibiotic therapy is wise, at least early in the treatment, until an infectious etiology has been ruled out. There is good logical reason to use ursodeoxycholic acid (15 mg/kg PO q24h) in these cats for its choleretic and antiinflammatory effect as well as its effect on modulating the bile acid pool and reducing toxic bile acids. Use of antioxidants such as S-adenosylmethionine (20 mg/kg or 200 to 400 mg total once a day on an empty stomach) and vitamin E (approximately 100 IU daily) is also logical because bile is a potent oxidizing toxin in the liver. However, none of these therapies has been critically evaluated in cats with lymphocytic cholangitis. Again, it is important to ensure that affected cats eat to prevent the development of concurrent hepatic lipidosis; as discussed in the preceding sections, a highly digestible, high-quality diet without protein restriction is indicated. A diet formulated for feline intestinal disease (such as Iam's feline intestinal or Royal-Canin feline selected protein or Hills ID) might be the most appropriate because of the relatively high prevalence of concurrent inflammatory bowel disease. Tube feeding should be considered if necessary, as outlined in the section on hepatic lipidosis. Cats with more acute signs, particularly associated with concurrent intestinal and/or pancreatic disease, may require hospitalization and IV fluid therapy.

The prognosis for cure appears to be poor because the disease appears to wax and wane chronically in spite of treatment. However, few cats with lymphocytic cholangitis die as a result of their disease. This is likely because, unlike in dogs, the disease does not generally progress to end-stage cirrhosis.

## **Sclerosing Cholangitis**

Sclerosing cholangitis, or biliary cirrhosis, involves an endstage fibrotic liver, and is very uncommon in cats. The condition is characterized histologically by diffuse proliferative fibrosis of bile duct walls spreading to involve the hepatic lobules and disrupting their architecture and circulation. It is thought in most cases to represent an end stage of chronic biliary tract disease: usually complete obstruction or chronic severe liver fluke infestation (see the next section). It is very unusual for neutrophilic or lymphocytic cholangitis to progress to sclerosing cholangitis in cats. Affected cats present with typical clinical signs of chronic biliary tract disease, as outlined in the cholangitis and extrahepatic biliary tract obstruction sections. Affected cats may also develop chronic portal hypertension, with the resultant development of ascites, gastrointestinal ulceration, and/or acquired portosystemic shunts (PSS) and hepatic encephalopathy (see Chapter 39). Acquired PSSs are much less common in cats

than in dogs, although they are occasionally recognized. Sclerosing cholangitis is diagnosed on hepatic biopsy; again, it is very important to evaluate hemostasis profiles before biopsy and to administer vitamin K (0.5 mg/kg SQ or IM q12h for up to 3 days) as necessary because vitamin K deficiency is common in cats with chronic biliary tract obstruction. It should be noted that cats with sclerosing cholangitis may have hepatomegaly on radiography, which is unexpected (cirrhosis usually results in a small liver in dogs). Presumably, this reflects the biliary tract dilation and florid peribiliary fibrosis in these cases. Treatment is supportive, with treatment of only the clinical signs associated with portal hypertension, as outlined in Chapter 39.

## Liver Fluke Infestation

## **Etiology and Pathogenesis**

Liver fluke infestation is regularly observed in cats from areas endemic for the family Opisthorchiidae (Platynosomum spp. and also occasionally Amphimerus pseudofelineus and Metametorchis intermedius). It is estimated that in Florida and Hawaii Platynosomum fastosum (the most common feline liver fluke) has prevalence of up to 70%; the clinical feline disease is referred to as "lizard poisoning." The flukes require two intermediate hosts: water snails and lizards, amphibians, geckos, or fish, depending on the species. The cat is the final host and is infested by ingesting the metacercariae in the second intermediate host. The immature flukes migrate from the intestine to the liver via the bile ducts and become adult and patent by 8 to 10 weeks. Eggs can then be found in the feces (inconsistent) or bile aspirates (more reliable). The severity of associated disease seems to depend on the parasite load and on individual responses. Many cases are mild. In some cases the pancreas may also be affected. The clinical signs are caused by peribiliary inflammation and fibrosis in the liver, culminating, in severe cases, in effectively a posthepatic jaundice. The fluke takes 8 to 12 weeks from infestation to reach adulthood. In experimental infestations hepatic lesions are visible histologically from 3 weeks postinfestation. There is an initial distention of proximal bile ducts and a neutrophilic and eosinophilic inflammatory response, which progresses chronically to adenomatous hyperplasia of ducts and surrounding florid fibrosis. Eosinophils may be absent in the later stages of disease, and flukes and eggs may not be seen on histology.

## **Clinical Signs**

Commonly, cats with low-grade infestations remain asymptomatic. However, heavy infestations can be associated with severe and often fatal disease (Haney et al., 2006; Xavier et al, 2007). In these cases clinical signs are typically those of posthepatic jaundice combined with inflammatory liver disease (e.g., jaundice, anorexia, depression, weight loss, and lethargy). Diarrhea and vomiting have been features of clinical cases but do not occur in experimental cases; affected cats may also have hepatomegaly and ascites.

### Diagnosis

Diagnosis is made after a history of exposure (cats often have a history of hunting lizards) combined with finding the flukes or eggs in feces and bile. Supportive findings are high liver enzyme activities typical of cholestasis; ALT and AST activities and bilirubin concentration are particularly high, but ALP activity is surprisingly often only mildly elevated. Eosinophilia may be seen in severe cases but is inconsistent. Ultrasonography reveals changes typical of biliary tract disease, such as dilation of the bile ducts. In one case fluke infestation also caused acquired polycystic disease of the biliary system (Xavier et al., 2007).

Ova may be found in the feces using the formalin-ether sedimentation method (Box 37-3). However, shedding of eggs is sporadic; also, of course, eggs will not be present if the fluke infestation has resulted in a complete biliary obstruction. The most reliable way of demonstrating flukes and eggs is on bile aspirates.

## Treatment

The ideal and most effective treatment regimen for feline liver flukes remains controversial. Currently, the most commonly recommended treatment is praziquantel at 20 mg/kg SQ q24h for 3 days. The prognosis for recovery in severely affected cats is poor.

## **CHOLECYSTITIS**

Cholecystitis refers to inflammation of the gallbladder. Neutrophilic cholecystitis is frequently seen in cats but rarely in



BOX 37-3

Formalin-Ether Sedimentation Technique for Detecting Platynosomum concinnum Ova in Feces

- Mix 1 g of feces in 25 ml saline; filter through a fine mesh screen.
- 2. Centrifuge solution for 5 min at 1500 rpm; discard the supernate.
- Resuspend the pellet with 7 ml of 10% neutral buffered formalin; let stand for 10 min.
- Add 3 ml of cold ether on top of solution and shake vigorously for 1 min. Centrifuge for 3 min at 1500 rpm.
- Discard the supernate, resuspend the pellet in several drops of saline, and prepare slide of solution to examine microscopically.

dogs. It may occur alone or in combination with neutrophilic cholangitis. Ultrasonographically, the gallbladder wall often appears thickened and sometimes irregular; there may be "sludging" of the bile and/or choleliths. Clinical signs, diagnosis, and treatment are very similar to those of neutrophilic cholangitis (see preceding section). Lymphocytic cholecystitis is also occasionally recognized.

### **BILIARY CYSTS**

Most cystic lesions in the feline liver are of bile duct origin and may be congenital or acquired. Congenital cysts are usually multiple and often present as part of a polycystic disease of several organs, including the kidneys. The cystic contents are clear. Persian cats and Persian crosses are at increased risk. Cysts may be an incidental finding on imaging, particularly if they are small, but large cysts can cause clinical signs as a result of destruction of hepatic tissue and also compression of surrounding bile ducts resulting in signs of biliary tract obstruction (see next section). Treatment is not indicated if they are small and nonprogressive, but if they are large and causing problems, they may be treated surgically by removal or omentalization (Friend et al., 2001).

Acquired hepatic cysts may be single or multiple and may be small or very large. The contents may be clear, bloody, or bilious. They may occur secondary to trauma, inflammation, or neoplasia (including biliary cystadenomas) or in rare cases caused by liver flukes. Therapy depends on the cause, but surgical management may be necessary if they are large.

## EXTRAHEPATIC BILE DUCT OBSTRUCTION

## Pathogenesis and Etiology

Extrahepatic bile duct obstruction (EBDO) is a syndrome associated with several different underlying causes. Causes of EBDO may be categorized as extraluminal compressive or intraluminal obstructive lesions, but often diseases cause EBDO through a combination of these mechanisms (e.g., cholangitis may result in a combination of extraluminal compression by associated edema and inflammation and intraluminal obstruction by inspissated bile). Therefore it is more practically helpful to divide the causes into common and less common causes (Box 37-4). Several studies have shown inflammation of the small intestine, pancreas, biliary tract, or a combination of these ("triaditis") to be the most common cause of EBDO in cats; neoplasia of the biliary tract or pancreas are the next most common cause. Choleliths are very uncommon in cats. Those reported in the literature are usually cholesterol or calcium salts or a mixture of these and are associated with cholangitis. They are variably radiodense depending on the amount of calcium in the stone, but they are easily visualized with ultrasonography of the biliary tract. Two out of the three cases of bilirubin choleliths reported in the literature were from Somali cats with pyruvate kinase deficiency, and it was assumed that they were secondary to hemolysis (Harvey et al., 2007). Therefore finding bilirubin



Causes of Extrahepatic Bile Duct Obstruction (EBDO) in Cats

#### Common Causes

- One or a combination of inflammation of pancreas, duodenum, or biliary tree (most common)
- Neoplasia, particularly of the biliary tree or pancreas (second most common)

#### **Less Common Causes**

- Stricture of bile duct after inflammation, surgery, or trauma
- Diaphragmatic hernia with involvement of the gallbladder/common bile duct and subsequent compression
- Cholelithiasis
  - Usually cholesterol and/or calcium salts secondary to cholangitis
  - Occasionally bilirubin—associated with pyruvate kinase deficiency-induced hemolysis in Somali cats
- Cysts (congenital or acquired) compressing biliary tree
- Liver flukes

Note that sepsis distant to the liver can produce an associated biliary stasis, which may appear clinicopathologically to be very similar to EBDO.

Note also that biliary tract rupture (usually traumatic) produces similar clinicopathological findings to EBDO.

choleliths in a cat should stimulate a search for underlying hemolytic disease.

#### **Clinical Features**

In case series of cats with EBDO, clinical signs, clinicopathologic findings, and survey radiographic findings were indistinguishable from those associated with other severe cholestatic hepatopathies; jaundice, anorexia, depression, vomiting, and hepatomegaly were the main presenting features. If biliary obstruction is complete, feces will be pale or acholic. There may be a cranial abdominal mass on palpation, because of either a very distended gallbladder or underlying neoplasia, but often abdominal palpation is normal (other than the hepatomegaly). Cats with EBDO are at particular risk of malabsorption of fat-soluble vitamins, including vitamin K, because of the lack of intestinal bile salts reducing fat digestion. This is compounded in many cases by the concurrent intestinal and/or pancreatic disease, which further reduces fat absorption. As discussed previously, it is very important in these cases to assess coagulation times before performing biopsies or surgery and to supplement vitamin K parenterally as necessary.

#### Diagnosis

Ultrasonography is the most useful diagnostic tool to differentiate EBDO from other biliary tract diseases in cats; sometimes, the cause of EBDO is determined. Clinicopatho-

logic findings are nonspecific; the high concentration/activities of hepatocellular and biliary enzymes, bilirubin, and cholesterol resulting from cholestasis are indistinguishable from those in cats with other severe cholestatic hepatopathies. Ultrasonography will usually reveal dilation of the gallbladder and the extrahepatic and intrahepatic biliary trees, although gallbladder dilation is not a consistent and essential finding. A search should then be conducted for a possible cause of obstruction by carefully examining the small intestine, liver, and pancreas for evidence of inflammation or neoplasia. Biliary tract rupture can present in a similar way and should be ruled out by identifying and analyzing any free abdominal fluid; cats with biliary rupture have a high concentration of bilirubin in the fluid. FNA of bile from the gallbladder under ultrasonographic guidance should be avoided or approached with great care if EBDO is suspected or confirmed because there is a high risk of leakage on account of the increased pressure. In these cats it is preferable to aspirate bile during surgery. It may be necessary to undertake an exploratory laparotomy to assess bile duct patency and the cause of the obstruction. Hemostatic function should be assessed first, and vitamin K therapy given as 0.5 mg/kg of vitamin K<sub>1</sub> SQ or IM q12h for 3 days. The liver, pancreas, and small intestine should be carefully inspected and biopsied, as deemed necessary.

#### **Treatment**

Treatment depends on the underlying cause of the EBDO and whether the obstruction is complete or partial. Biliary tract surgery in the cat carries a high morbidity and mortality and should be undertaken only when necessary to relieve complete obstruction. The prognosis for partial obstructions is surprisingly good when using medical management, and surgery may not be necessary in all cases. Recent studies of EBDO in acute-on-chronic pancreatitis in humans suggest that medical management rather than surgery or stenting is the treatment of choice in most cases and that there are usually no long-term sequelae. Similar studies have not been reported in cats.

If the feces are not acholic and there is some evidence of bile flow into the duodenum, cats can be managed medically with a choleretic (ursodeoxycholic acid 15 mg/kg PO q24h) and an antioxidant such as S-adenosylmethionine (20 mg/kg or 200 to 400 mg daily on an empty stomach) to protect the hepatocytes against bile-induced oxidant damage. The underlying disorder should also be treated as outlined in the preceding section. However, if the cat does not improve after several days or signs of complete obstruction, such as acholic feces, develop, surgical intervention is indicated. If the cat requires cholecystoenterostomy, the prognosis is poor.

## HEPATIC AMYLOIDOSIS

#### Etiology

Hepatic amyloidosis is an uncommon but apparently emerging cause of liver disease in cats. Historically, amyloidosis has

been recognized most commonly as a familial disease in Siamese cats with both renal and hepatic involvement. Abyssinian cats also suffer from familial amyloidosis, but it is predominantly renal in this breed. However, more recently it has been reported sporadically in a number of breeds, including domestic short-haired cats with purely hepatic and no renal involvement (Beatty et al., 2002). The amyloid in both familial and sporadic cases is amyloid A (inflammatory), and in sporadic cases there is usually an underlying chronic inflammatory process in another organ (such as chronic gingivitis) thought to be the driving force for the formation of the inflammatory amyloid.

## **Clinical Signs and Diagnosis**

Affected cats usually present with signs of anemia and hypotension related to rupture of the hepatic capsule and hemoabdomen. These cats are predisposed to hepatic rupture because the liver is enlarged and also rigid and therefore easily damaged with normal trauma such as knocking the abdomen when jumping. Affected cats usually exhibit lethargy, anorexia, pale mucous membranes, a bounding pulse, and a heart murmur secondary to the anemia but rarely any specific signs of liver disease. There may be hepatomegaly on abdominal palpation.

## **Diagnosis**

Diagnosis relies on histopathology of a liver biopsy; although clinicopathologic and ultrasonograhic findings are supportive, it is important to rule out the major differential diagnoses of FIP, hepatic lipidosis, and hepatic lymphoma. The transient anemia resolves as blood is reabsorbed from the abdomen (autotranfusion). There are mild to marked increases in ALT activity and globulin concentration but rarely increases in ALP and GGT activities, which helps differentiate amyloidosis from biliary tract disease and lipidosis. On ultrasonography amyloidosis can resemble both lymphoma and lipidosis, with hepatomegaly and a generalized increase in hepatic parenchymal echogenicity or mixed hypo- and hyperechoic appearance (Beatty et al, 2002), but no dilation of the biliary tract. FNA cytology is not helpful because amyloid does not appear on the aspirate. Therefore hepatic biopsy, after careful evaluation of hemostasis profiles, is the recommended method of diagnosis.

### **Treatment and Prognosis**

Treatment is supportive because there is no specific antiamyloid medication. Colchicine is of uncertain efficacy and is not indicated in cats because of its potential toxicity. Instead, the focus should be on reducing or eliminating the underlying inflammatory disorder driving the amyloid deposition, and supportive care with antioxidants and vitamin K supplementation as necessary (0.5 mg/kg SQ or IM every 7 to 20 days). Blood transfusions may be necessary in cats with acute hemoabdomen. The long-term prognosis is poor, and most cats die as a result of intraabdominal bleeding.

## **NEOPLASIA**

## Etiology

Primary liver tumors are uncommon in cats but are nevertheless more common than in dogs. Hepatic tumors are much less common in both species than they are in people, possibly because two of the predisposing factors for development of liver tumors (hepatitis virus infection and α-protease inhibitor deficiency) have not been recognized in small animals. Cirrhosis also predisposes to liver tumors in people but is rare in cats. Liver tumors represent 1% to 2.9% of all neoplasms in cats (Liptak, 2007) but up to 6.9% of the nonhematopoietic tumors. No predisposing factors have been identified. In contrast to dogs, benign tumors are more common than malignant tumors in cats; they may be an incidental finding during workup for other diseases. An unusual benign tumor occasionally found in cats is the myelolipoma, which has a suggested association with chronic hypoxia and hepatic involvement in diaphragmatic hernias. Biliary carcinomas are the most common malignant tumors in cats; this may mirror the high prevalence of biliary tract disease in this species. Trematodes are also a predisposing cause in humans and may be in some cats, but bile duct carcinomas also occur in cats outside the range of liver fluke infestations, so there are obviously other factors involved. Also in contrast to dogs, primary hepatobiliary tumors are more common than metastatic neoplasia in cats. Secondary tumors include particularly hematopoietic tumors, such as lymphoma and, less commonly, leukemias, histiocytic tumors, and mast cell tumors and metastases from other organs such as the pancreas, mammary glands, and gastrointestinal tract. Hemangiosarcomas in the liver may be primary or secondary, and sometimes the origin is difficult to ascertain if multiple organs are involved, although primary hepatic hemangiosarcomas appear to be more common in cats than in dogs.

The common feline primary liver tumors recognized and their behavior are outlined in Table 37-4.

#### **Clinical Features**

Primary malignant liver tumors are usually seen in older cats (mean age 10 to 12 years). There is no obvious gender predisposition reported. The presenting clinical signs and clinicopathologic findings are indistinguishable from those in cats with other primary liver diseases. There may be lethargy, vomiting, weight loss, ascites, or jaundice. Some affected cats may have palpable hepatomegaly, ascites, or liver masses on abdominal palpation. However, at least 50% of cats with liver tumors are asymptomatic.

## Diagnosis

Diagnosis relies on a combination of diagnostic imaging, cytology, and histology. A suspicion may be gained from the clinical findings, but given that more than half of affected animals have no clinical signs, the liver mass may be a serendipitous finding while the cat is being imaged for another reason. On clinical pathology high liver enzyme activity and bile acid concentration and mild anemia and neutrophilia are common but nonspecific findings. Jaundice is uncommon but can occur. Liver function is usually normal because the tumor must involve more than 70% of liver mass before resulting in a reduction in liver function. The exception to this is diffuse hematological malignancy (e.g., lymphoma), which can result in significant disturbance of hepatocyte function (including coagulopathies). The functional defects often resolve when the tumor is cytoreduced by chemotherapy.

Radiographs may show hepatomegaly; the liver may have an irregular border or focal enlargement of one lobe. There may be also involvement of other organs (e.g., lymphadenopathy in cats with lymphoma), and thoracic radiographs may reveal evidence of metastases. However, radiographs



**TABLE 37-4** 

**Primary Liver Tumors in Cats** 

### TYPE OF TUMOR

Bile duct tumors:

Biliary carcinoma (including cystadenocarcinoma)

Biliary adenoma

Gallbladder tumors

Hepatocellular tumors:

Hepatocellular carcinoma (HCC)

Hepatocellular adenoma (hepatoblastoma-very rare)

Neuroendocrine tumors:

Hepatic carcinoid

Primary hepatic sarcomas:

Hemangiosarcoma, leiomyosarcoma, and others

#### BEHAVIOR

Most common primary liver tumor in cats (>50%).

Biliary carcinoma most common malignant feline liver tumor. Aggressive behavior—diffuse intraperitoneal metastases in 67% to 80% of cases.

Recognized but less common than biliary tumors. Adenoma more common than carcinoma.

Very rare but very aggressive

Uncommon. Most locally aggressive and high MR.

Hemangiosarcoma most common primary hepatic sarcoma in cats.

Note: Benign tumors are more common than malignant tumors in this species. MR. Metastatic rate.

may also be normal. Some malignant hepatic tumors commonly metastasize to the peritoneum and local lymph nodes and less commonly to the lungs. As in other diseases of the liver, ultrasonography is more helpful in identifying a hepatic mass and also in evaluating for metastases; it also allows for FNA of the mass(es). Hepatic tumors can also be cystic, particularly cystadenocarcinomas. Cats, unlike dogs, rarely have benign nodular hyperplasia in the liver, so this is not a differential diagnosis for a hepatic mass. Diffuse hepatic tumors (e.g., lymphoma) may show a diffuse change in echogenicity, or the liver may appear normal on ultrasonography. Important differential diagnoses for diffuse hepatic tumors are FIP, lipidosis, and amyloidosis. A thorough abdominal ultrasonographic examination should be undertaken to search for evidence of metastases. It should be kept in mind that because benign tumors are more common than malignant tumors in cats, no animal should be euthanized on the basis of finding a hepatic mass with no evidence of metastases on ultrasonography.

A definitive diagnosis is usually obtained using cytology or histopathology. In some cases FNAs may be diagnostic, but in others they may be difficult to interpret, particularly in cats with benign hepatocellular tumors, in which the cells look indistinguishable from normal hepatocytes. Ultrasonography-guided Tru-Cut biopsies are usually diagnostic; alternatively, biopsies can be obtained during laparoscopy or laparotomy. In the case of an apparently single lesion, the clinician may elect to proceed straight to surgical removal and an "excisional" biopsy. Hemostasis profiles should be evaluated before performing a biopsy. It is unusual for the one-stage prothrombin time and activated partial thromboplastin time to be prolonged in cats with primary liver tumors, but they can be markedly prolonged in cats with diffuse hepatic infiltration with lymphoma or other diffuse secondary tumors (e.g., mast cell tumors). Biopsies should not be considered in these cases until clotting factors have been replenished with a fresh frozen plasma transfusion.

#### **Treatment**

Treatment of primary hepatic tumors relies on surgical removal if they are resectable. This is advisable even in cats with benign tumors, including biliary adenomas. Treatment of diffuse, nodular, or metastatic tumors may be difficult. Primary hepatic tumors generally have a poor response to chemotherapy. It has been suggested that this is because hepatocytes, both normal and transformed, have high expression of the multidrug resistance membrane-associated P-glycoprotein and also that hepatocytes are naturally high in detoxifying enzymes. Radiotherapy is not wise because normal liver tissue is very radiosensitive. For additional information, please see Chapters 80 (the section on lymphoma) and 82 (the section on mast cell tumors).

#### **Prognosis**

Prognosis of benign tumors is good after resection. Prognosis is very poor for cats with any type of malignant liver

tumor; however, most cats with lymphoma of the liver respond to chemotherapy (see Chapter 80).

## **CONGENITAL PORTOSYSTEMIC SHUNTS**

## **Etiology and Pathogenesis**

PSSs are abnormal vascular communications between the portal and systemic circulation. They may be congenital or acquired secondary to portal hypertension. Those of the latter type are usually multiple vessels and are very rare in cats because they usually occur secondary to severe hepatic fibrosis and cirrhosis, both uncommon in cats. Acquired PSS secondary to a congenital hepatic arteriovenous (AV) fistula has been reported in a young cat, but this is very rare (McConnell et al., 2006). Most cases of PSS in cats are therefore congenital, but even these are recognized less commonly than in dogs. Congenital PSSs are usually single or at most double vessels and may be intrahepatic or extrahepatic in location. Cats may have either type of PSS (Lipscomb et al., 2007). Extrahepatic PSSs represent abnormal communcations between the portal vein or one of its contributors (left gastric, splenic, cranial, or caudal mesenteric or gastroduodenal veins) and the caudal vena cava or azygos vein. Intrahepatic PSSs may be left-sided, in which case they are believed to represent a persistence of the fetal ductus venosus after birth (patent ductus venosus, PDV; White and Burton, 2001), or they may be right-sided or centrally located in the liver, in which case they are believed to be anomalous vessels. The reason that congenital PSSs develop at all is unknown, although it is assumed that there may be genetic reasons and/or developmental problems in utero that resulted in abnormal development of the liver vasculature.

The pathophysiology of congenital PSS largely relates to the shunting of unfiltered blood directly into the systemic circulation, resulting in hyperammoniemia and hepatic encephalopathy (HE). The pathophysiology of HE is outlined in Chapter 35. The shunting vessel acts as a lowresistance pathway for some of the portal blood, bypassing the higher resistance intrahepatic portal vasculature. Portal pressure is therefore lower than normal in cats with congenital PSS, which is an important distinguishing feature from (rare) cases of acquired shunting, in which there is portal hypertension and therefore an increased portal pressure. Concurrent hepatic microvascular dysplasia or portal vein hypoplasia, which can confuse this differentiation, occurs in some dogs (see Chapter 38) but has not been reported in cats. Shunting may also allow bacteremia and potentially infections of hematogenous origin that may present as "pyrexia of unknown origin," although this is rare. Additional effects of portal blood bypassing the liver are hepatic atrophy and a reduction in the metabolic activity of the liver, which contributes to inefficient use of dietary components, poor growth, and loss of lean body mass.

Liver atrophy (microhepatia) and changes in hepatic organelle function are partly due to changes in hepatic per-

fusion. The portal blood usually provides about 50% of the liver's oxygen requirement, but this is obviously reduced in cats with PSS. Cats with PSS typically have arteriolar hyperplasia in an attempt to compensate for the reduced portal flow, but they often still have some degree of hepatic underperfusion. In addition, PSS results in reduced delivery of "hepatotrophic factors," such as insulin, to the liver, which further contributes to hepatic atrophy.

## **Clinical Features**

Persian and Himalayan cats have been reported to be at increased risk for congenital PSS in small case series, and another series noted that purebred cats in general were overrepresented; however, cats of any breed, including mixed-breed cats, can be affected. Both sexes appear to be equally at risk. There is no reported associated between breed and shunt types (unlike in dogs), although in one study 6 out of 13 cats with an intrahepatic PSS were Siamese (Lipscomb et al., 2007). Most cases present before 2 years of age; many are younger than 1 year old, but old cats with congenital PSSs are frequently recognized.

The typical clinical signs in cats with congenital PSS are gastrointestinal, urinary, or neurological (HE), although the latter tend to predominate in cats and, anecdotally, are often more severe than in dogs. Cats typically present with a history of waxing and waning neurological signs consistent with HE rather than a sudden acute HE crisis. The typical signs of HE are outlined in Box 35-1. Hypersalivation is a common sign of HE in cats, but it is rare in dogs. There is sometimes an association between HE and feeding, which may relate to glutamine metabolism by enterocytes releasing ammonia, although not all cats display these signs. Cats in acute crisis may present comatose or with seizures; cats appear to be more susceptible to seizures than dogs, both preoperatively and postoperatively. The reason for this is unknown, although it has been suggested that sudden changes in the concentrations of ammonia and other metabolites in the blood after surgery or sudden changes in medical management may destabilize neurotransmitters in cats. Drug intolerance is common, particularly prolonged recovery from routine anesthesia for spaying/neutering. Animals with PSS may also show intermittent vomiting and/or diarrhea. Urinary tract signs are due to cystitis associated with urate calculi and polyuria/polydipsia, but they are less common in cats than in dogs. Impaired urine-concentrating ability may reflect reduced renal-concentrating gradient secondary to low urea concentration and increased blood cortisol concentration secondary to reduced hepatic breakdown, although this has been demonstrated only in dogs thus far. Cats with congenital PSS also often (but not always) show signs of poor growth compared with their littermates (Fig. 37-9). There has been a reported high prevalence of coppercolored irises in cats with PSS (see Fig. 37-9), but this is not a consistent feature.

Because of the low portal pressure, ascites is not a feature in cats, which helps in distinguishing congenital PSS from



A 6-month-old kitten with a congenital portosystemic shunt, demonstrating very small size for its age and also coppercolor irises, which are often noted in kittens with portosystemic shunts.

the rare feline cases of acquired PSS, in which ascites is more common because of portal hypertension.

## **Diagnosis**

A suspicion for congenital PSS can be gained from the history of recurrent neurological signs combined with high fasting and/or postprandial bile acid or ammonia concentrations. Care should be taken when performing traditional ammonia tolerance tests, which can precipitate severe HE. Postprandial ammonia or bile acid determinations are safer alternatives. Serum bile acid concentrations should be measured before and 2 hours after feeding. (see Box 36-1). If ammonia is measured instead, the postprandial sample should be taken 6 hours after feeding (Walker et al., 2001). Other typical (but not pathognomonic) clinicopathologic findings in some (but not all) cats include low serum urea concentration, mildly increased liver enzyme activities, and microcytosis. Notable differences from dogs are that decreases in total protein or albumin concentrations, hypoglycemia, and anemia are much less common in cats. Urine specific gravity is low in many dogs but occurs in fewer than 20% of affected cats. If fasting bile acid concentrations are very high, it is not necessary to obtain a postprandial sample, but the diagnostic sensitivity of doing both is higher than just measuring fasting concentrations. If biliary stasis (which also causes high bile acid concentrations) is ruled out and the cat does not have hepatic lipidosis (which causes hepatocellular failure and HE with increases in bile acid and ammonia concentration in many cases), it is likely that the cat has a congenital PSS because other causes of HE and high bile acid concentrations are uncommon in cats. Abdominal radiographs show a small liver in 50% of cases (Lamb et al., 1996). However, for definitive diagnosis the shunting vessel must be visualized.

Visualization of the shunting vessel is achieved by ultrasonography or portal venography (see Fig. 36-7, A and B) Transcolonic portal scintigraphy will also demonstrate portosystemic shunting, but it does not differentiate congenital from acquired shunting. A liver biopsy should be taken at the time of surgery or portovenography (after evaluation of hemostasis profiles) to rule out other or concurrent conditions. This shows histological features very similar to those in dogs and typical of portal venous hypoperfusion with loss of smaller portal veins, increased numbers of arterioles, hepatocellular atrophy with lipogranulomas, and sometimes periportal sinusoidal dilation but minimal inflammation.

#### **Treatment**

Treatment involves complete or partial ligation of the shunting vessel using one of several methods, including silk or cellophane or ameroid constrictors; a detailed explanation is beyond the scope of this book. The procedure is best reserved for referral centers, particularly in cats, which are more prone to complications than dogs. The postoperative mortality in cats appears to be higher than in dogs, which is often due to intractable severe neurological signs. Pretreatment with phenobarbital has been attempted, but too few cases have been reported to assess its value. Propofol infusions are often used for HE-associated seizures in dogs, but care must be taken in cats because of their susceptibility to Heinz body anemia when given propofol infusions.

Cats should be managed medically before and for a period of about 2 months after surgery while the portal vasculature and liver mass recover. This involves careful mild dietary protein restriction with additional antibiotics (usually amoxicillin, 15 to 20 mg/kg PO q8h) and sometimes also a soluble fiber source such as lactulose (2.5 to 5 ml, given PO q8h to effect). Some anecdotal data suggest that changes in medical management should be made more gradually in cats than in dogs to prevent the risk of seizures (e.g., change the diet first, then add antibiotics after a week or more, and then add the soluble fiber source later). Details of medical management of HE are described in Chapter 39. Cats do not tolerate marked dietary protein restriction because of their high obligate protein requirement (see Table 37-2). A diet manufactured for cats with liver disease (such as Hills LD) is appropriate, and, unlike in dogs, home-made diets based on dairy protein should be avoided in cats because dairy protein is relatively deficient in arginine, which is essential for the urea cycle; deficiency will further predispose to hyperammonemia. Medical management alone is effective in some dogs long term (see Chapter 38), but anecdotally, cats do not do as well with medical management of congenital PSS, probably because of their high obligate protein metabolism, which would make them more susceptible to hyperammonemia, regardless of the diet fed.

#### **Prognosis**

The prognosis appears to be good if the PSS can be ligated, although insufficient cases have been reported to assess the



BOX 37-5

## Infectious Diseases with Hepatic Involvement in Cats

Liver fluke (see text for details)
Feline infectious peritonitis
Toxoplasmosis
Bartonellosis
Histoplasmosis
Tyzzer's disease
Salmonellosis

Infection with *Streptococcus* groups B and G in neonates Leptospirosis (extremely rare)
Disseminated mycobacterial infections
Infection with *Cytauxzoon felis* 

Tularemia (Francisella tularensis)

Note also that neutrophilic cholangitis is often due to ascending bacterial infection from the gut. *Bartonella* spp. may be involved in the etiology of some cases of lymphocytic cholangitis.

long-term prognosis. However, clients should be warned that short-term mortality rate after surgery is relatively high.

#### HEPATOBILIARY INFECTIONS

Several infectious organisms can infect the liver, either as a primary target or as part of a more generalized infection. These are listed in Box 37-5. In addition, neutrophilic cholangitis likely has a primary infectious cause in most cats (discussed in more detail in a previous section).

Hepatic involvement is common in both the dry and effusive forms of FIP (see Chapter 97). Because cats with effusive FIP can present with the same signs as cats with lymphocytic cholangitis, it is an important differential diagnosis for this disease. A liver biopsy may be necessary to distinguish them; a diagnosis is occasionally made cytologically.

Disseminated toxoplasmosis is uncommon in cats, but when it occurs, the liver is usually involved with intracellular growth of Toxoplasma gondii during the active clinical disease, resulting in cell death. Effects of delayed hypersensitivity reactions and immune-complex vasculitis also contribute to clinical illness. Infection of the lungs, liver, and central nervous system (including the eyes) with trophozoites is most commonly responsible for clinical signs. As expected, high serum ALT activity and hyperbilirubinemia commensurate with the degree of hepatocellular necrosis are the typical serum biochemical findings in cats with liver involvement. Cholangiohepatitis resulting from infection of the biliary epithelium has been noted occasionally in experimental and spontaneously occurring cases of toxoplasmosis in cats. The distribution of affected tissues in disseminated histoplasmosis often includes the lung, eye, bone marrow, spleen, lymph node, skin, bone, and liver. Infection with Bartonella spp. can cause cholangitis in cats.

## TOXIC HEPATOPATHY

## **Pathogenesis and Etiology**

By definition, toxic hepatopathy refers to a hepatic injury directly attributable to exposure to environmental toxins or certain therapeutic agents. Any therapeutic agent could potentially be heptatotoxic as a result of an idiosyncratic reaction, but only a limited number of such drugs have been reported in cats (Box 37-6) in addition to reported environmental hepatotoxins. Cats are particularly sensitive to phenol toxicity because of their limited hepatic glucuronide transferase activity. A variety of essential oils used topically have been reported to be hepatotoxic in cats. Essential oils are absorbed rapidly, both orally and dermally, and are metabolized by the liver to glucuronide and glycine conjugates; it is believed that cats are more sensitive than dogs to their hepatotoxic effects (Means, 2002).

Complete information that could support meaningful conclusions about the frequency, character, and substances that consistently cause hepatotoxicity in cats is not available. Clinicians therefore must rely on anecdotal reports, clinical observations, and data accumulated by central agencies such as the National Animal Poison Control Center in Urbana, Illinois (888-426-4435; \$55 per case via credit card), and the U.S. Food and Drug Administration's Center for Veterinary Medicine, in Washington, DC (the toll-free telephone number for reporting suspected adverse drug experiences is 1-888-FDA-VETS). In general, drug- or toxin-induced hepatic injury in cats is extremely uncommon, and most reactions are acute (occuring within 5 days of exposure). The character and severity of the toxic reaction depend on the characteristics of the substance, as well as the dose and the duration of exposure.

Three therapeutic agents have been reported to be hepatotoxic in certain cats: tetracycline (1 cat), diazepam (17 cats), and stanozolol (16 cats). Veterinarians have used these agents for years without known deleterious effects. For each drug, clinical and clinicopathologic signs of hepatotoxicosis developed within 13 days of daily oral administration at recommended dosages. The adverse hepatic reaction to tetracycline was serious but nonlethal, and the cat recovered completely after drug discontinuation and 6 weeks of supportive care (Kaufman et al., 1993). Histologic findings in the liver included centrilobular fibrosis, mild cholangiohepatitis, and mild lipid deposition in hepatocytes. In the cats that experienced diazepam-associated hepatic failure, the outcome was death in 16 of 17 despite intensive treatment. The oral dosages of diazepam that cats received, primarily for inappropriate urination, ranged from 1 mg every 24 hours to 2.5 mg every 12 hours. The histologic lesions in the liver were similar to those observed in the cat with tetracycline-associated hepatic injury but more severe: massive, predominantly centrilobular necrosis; suppurative cholangitis; and mild lipid vacuolation in some cats. Because of the severity of the lesions reported in cats apparently susceptible to diazepam-associated hepatic necrosis, serum liver enzyme activities should be evaluated during the window of days 3



BOX 37-6

Therapeutic Agents or Environmental Toxins that Can Cause Clinically Relevant Hepatic Toxicity in Cats

#### **Therapeutic Agents**

Acetaminophen 120 mg/kg

Griseofulvin

Megestrol acetate

Ketoconazole

Phenazopyridine

Aspirin >33 mg/kg/day

Tetracycline

Diazepam

Methimazole

Stanozolol

Nitrofurantoin

Amiodarone

MTP inhibitors (off-label use; see text)

Essential oils

#### **Environmental Toxins**

Pine oil + isopropanol

Inorganic arsenicals (lead arsenate, sodium arsenate,

sodium arsenite)

Thallium

Zinc phosphide

White phosphorus

Amanita phalloides (mushroom)

Aflatoxin

Dry-cleaning fluid (tricholorethane)

Toluene

**Phenols** 

to 5 of administration in cats given diazepam by mouth. Until there is more information that would improve understanding of this lethal and unpredictable hepatic reaction, use of other agents for control of behavior and elimination problems in cats is recommended. Cats that experienced an adverse reaction to stanozolol were healthy or had chronic renal failure (14 of 18 cats) or gingivitis/stomatitis (2 of 3 cats; Harkin et al., 2000). Serum ALT activity was markedly increased in most cats given 1 mg orally every 24 hours for several months or 4 mg orally every 24 hours (and 25 mg intramuscularly once) for 3 weeks; all but one survived after the drug was discontinued and intensive supportive care given. The histologic lesions were moderate to marked, diffuse centrilobular lipidosis and evidence of intrahepatic cholestasis (accumulation of bile and lipofuscin in hepatocytes and Kupffer cells).

The new microsomal triglyceride transfer protein (MTP) inhibitors marketed for weight loss in dogs are known to increase liver enzymes reversibly in that species but could result in clinically significant hepatic lipidosis in cats if used off-label in that species. This has not been reported yet because their use in cats is specifically contraindicated; however, clinicians should be aware of the risk.

The discriminatory eating habits of cats may account for the relatively uncommon occurrence of hepatotoxicity from ingested environmental toxins such as pesticides, household products, and other chemicals. It is certainly possible that many adverse hepatic reactions to drugs or toxic chemicals go unnoticed in cats because the first clinical signs of illness are vomiting and diarrhea, after which the medication is stopped. If the signs resolve, there usually is no further evaluation and the medication is not readministered to prove that the substance caused the reaction.

## Diagnosis

Clinical evidence that suggests drug- or toxin-induced hepatic damage includes supportive history (e.g., known exposure); normal liver size to mild generalized tender hepatomegaly; laboratory test results consistent with acute liver injury (e.g., high serum ALT and/or AST activity, hyperbilirubinemia); and, if the exposure was nonlethal, recovery with discontinuation of the agent and specific or supportive care. There are no pathognomonic histologic changes in the liver, although necrosis with minimal inflammation and lipid accumulation are considered classic findings. In many cases all clinical and clinicopathologic markers of a toxic liver insult are present, but the inciting chemical cannot be identified. In the case of hepatotoxicity from therapeutic agents, idiosyncratic reactions can occur that are not dose related, although drug overdose is usually the reason for liver injury.

#### **Treatment**

In cats with suspected acute hepatotoxicity, the basic principles for treatment of toxicoses are applied: preventing further exposure and absorption, managing life-threatening cardiopulmonary and renal complications, hastening elimination of the substance, implementing specific therapy if possible, and providing supportive care. Because few hepatotoxins have specific antidotes, the success of recovery often relies on time and aggressive supportive care. More guidance on supportive treatment of acute toxic hepatopathy is provided in Box 38-4.

Acetaminophen is one of the few toxins with a specific antidote. Acetaminophen is particularly toxic to cats, in which the usual hepatic detoxification pathways of sulphation and glucuronidation are particularly limited. Acetaminophen is oxidized to a toxic metabolite that causes methemoglobinuria within hours of ingestion and Heinz body anemia, hemolysis, and liver failure within 2 to 7 days of ingestion. N-acetylcysteine is a specific antidote that binds the toxic metabolite and increases the glucuronidation process. It should be administered at a dose of 140 mg/kg intravenously or orally as a loading dose and then continued at 70 mg/kg q6h for a total of seven treatments or for up to 5 days. There is also evidence that additional S-adenosylmethionine (20 mg/kg or 200 to 400 mg total daily) is beneficial in cats with acetaminophen toxicity because it replenishes glutathione, which inactivates the toxic metabolite (Webb et al., 2003).

# HEPATOBILIARY INVOLVEMENT IN CATS WITH SYSTEMIC DISEASE

Several feline systemic illnesses have hepatic manifestations that may be identified by physical, clinicopathologic, or radiographic examination, but the major clinical signs can be attributed to another disease (see Table 37-1). In such cases the hepatic lesion should recede with satisfactory treatment of the primary illness.

Metastatic neoplasia could be the underlying reason for abdominal enlargement resulting from hepatomegaly or, rarely, malignant abdominal effusion, although primary neoplasia is more common than metastatic neoplasia in the feline liver. Some of the signs of hyperthyroidism, especially occasional vomiting, diarrhea, and weight loss, can resemble those of primary hepatobiliary disease. Thyrotoxic cats commonly have high liver enzyme activities; more than 75% of affected cats have high serum AP activity (twofold to twelvefold), although in cats it is not known whether this is of liver or bone origin or, as is true for hyperthyroid human patients, both. More than 50% of hyperthyroid cats have high serum ALT or AST activity (twofold to tenfold). More than 90% of affected cats have high serum activity of at least one of the enzymes AP, ALT, and AST. Approximately 3% are hyperbilirubinemic. Histopathologic changes are minimal, and there appears to be little functional disturbance. It is thought that malnutrition, hepatocellular hypoxia, and the direct effects of thyroid hormone on liver cells are responsible for these liver-related abnormalities. Hepatomegaly associated with mild to moderate lipid deposition is a common physical examination finding in cats with diabetes mellitus; a small number of cats may also be icteric. Mild to moderate increases in liver-specific enzyme activities are typical. More severe clinicopathologic abnormalities might be expected in cats with more severe hepatic lipidosis. Hyperadrenocortism is rare in cats, and, unlike in dogs, obvious liver involvement is unusual. The liver is usually normal in size on radiographs, and it is unusual to identify high serum AP and ALT activities in hyperadrenocorticoid cats. Unlike dogs, cats do not possess a steroid-induced isoenzyme of ALP, and increased ALT, when recognized, is probably related to intercurrent diabetes mellitus.

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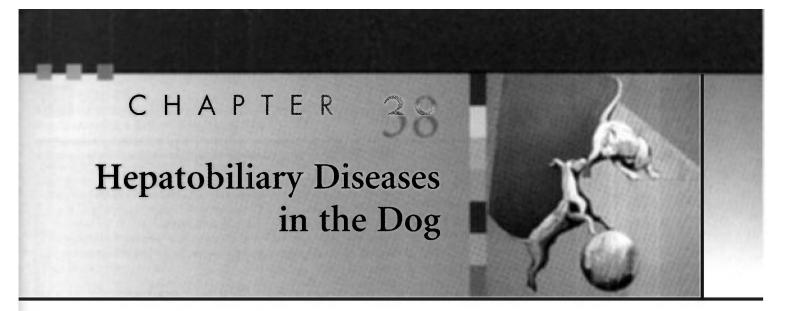
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## CHAPTER OUTLINE

# GENERAL CONSIDERATIONS CHRONIC HEPATITIS

Idiopathic Chronic Hepatitis Copper Storage Disease Infectious Causes of Chronic Hepatitis Lobular Dissecting Hepatitis Toxic Causes of Chronic Hepatitis

## ACUTE HEPATITIS

BILIARY TRACT DISORDERS

Cholangitis and Cholecystitis
Gallbladder Mucocele
Extrahepatic Bile Duct Obstruction
Bile Peritonitis

### CONGENITAL VASCULAR DISORDERS

Congenital Vascular Disorders Associated with Low Portal Pressure: Congenital Portosystemic Shunt Congenital Vascular Disorders Associated with High Portal Pressure

Dysplasia/Noncirrhotic Portal Hypertension FOCAL HEPATIC LESIONS

Abscesses

Nodular Hyperplasia

Neoplasia

HEPATOCUTANEOUS SYNDROME/SUPERFICIAL NECROLYTIC DERMATITIS

SECONDARY HEPATOPATHIES

Hepatocyte Vacuolation

Hepatic Congestion/Edema

Nonspecific Reactive Hepatitis

### **GENERAL CONSIDERATIONS**

There are marked differences between dogs and cats in the causes, types, and presentations of liver disease (see Table 37-2). In dogs chronic liver disease is more common than acute disease, and notably, chronic parenchymal disease (chronic hepatitis) is much more common in dogs than cats;

it almost invariably leads to progressive fibrosis and cirrhosis. This contrasts with cats, in which primary biliary disease is more common and fibrosis and cirrhosis extremely uncommon. The clinical signs of liver disease in dogs therefore tend to be even more nonspecific than in cats—jaundice is less common in association with parenchymal disease, and, because of the enormous reserve capacity of the liver, signs may not be seen until 75% of the liver mass is lost. The cause of chronic hepatitis in dogs is usually unknown, with a few notable exceptions, and treatment focuses on attempting to slow progression of disease and treating the clinical signs. Dogs with chronic hepatitis often develop portal hypertension, and treatment of the associated complications are central to treatment of disease in dogs (see also Chapter 39), whereas portal hypertension is very uncommon in cats. Congenital portosystemic shunts (PSSs) are more commonly recognized in dogs than in cats; in addition, vacuolar and secondary hepatopathies are very common in dogs and can be confused with primary liver disease on presentation. The most common primary and secondary liver diseases in dogs are outlined in Table 38-1.

## **CHRONIC HEPATITIS**

Chronic hepatitis is predominantly a histological definition. It is defined by the World Small Animal Veterinary Association (WSAVA) Liver Standardization group as being characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory cell infiltrate, regeneration, and fibrosis (Van Den Ingh et al., 2006; Fig. 38-1). The histological definition says nothing about temporal chronicity, and some authors have suggested that increases in liver enzyme activities for more than 4 months associated with inflammatory liver disease might constitute a definite diagnosis of "chronic" hepatitis in dogs.

Chronic hepatitis is common in dogs and shows some noticeable breed predilections, suggesting a genetic basis to the disease. Box 38-1 lists dog breeds reported to have a high prevalence of chronic hepatitis, and Box 38-2 lists possible reasons for genetic increases in susceptibility, all of which



TABLE 38-1

Liver Diseases in Dogs

PRIMARY	

Chronic hepatitis
Copper storage disease

Congenital portosystemic shunt Drug/toxin-induced hepatopathy

#### **SECONDARY**

Steroid-induced hepatopathy

Hepatic steatosis (lipidosis) (secondary to diabetes mellitus or hypothyroidism)

Congestion: heart failure or heartworm disease

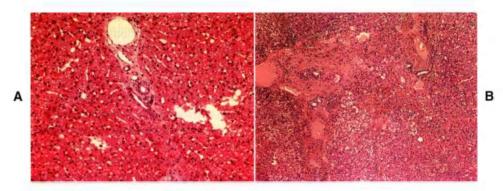
"Idiopathic" vacuolar hepatopathy in Scottish Terriers and others Reactive hepatitis (secondary to pancreatitis, inflammatory bowel disease, etc.)

Metastatic neoplasia

#### **UNCOMMON OR RARE**

Biliary tract disease, all types
Hepatic infections (see text)
Portal vein hypoplasia/microvascular dysplasia
Hepatic arteriovenous fistula
Acute fulminant hepatitis (all causes)
Hepatic abscess
Primary neoplasia

Hepatocutaneous syndrome



#### FIG 38-1

 $\bf A$ , Histopathology of normal liver from a middle-aged Yorkshire terrier. Note normal portal triad with hepatic portal vein, artery, and bile duct and hepatocytes arranged in neat cords with sinusoids between (white holes in bottom right are a sectioning artefact) Hematoxylin and eosin  $\times 200$ .  $\bf B$ , Histopathology of liver in a 3-year-old female English Springer Spaniel with severe chronic hepatitis. There is marked distortion of the normal lobular structure (compare to  $\bf A$ ) with inflammation and fibrosis and hepatocyte vacuolation and necrosis. There is also some ductular hyperplasia and disruption of the limiting plate. Hematoxylin and eosin  $\times 100$ . (Courtesy the Pathology Department, Department of Veterinary Medicine, University of Cambridge.)

have been demonstrated in humans with chronic hepatitis and some of which have been recognized in other diseases in dogs. Young to middle-aged dogs are most commonly affected, and the sex ratio varies among breeds. It should also be noted that there are some notable geographical differences in breed-related liver diseases, which likely reflect differences in breeding in different countries: Diseases common in the United States may be unusual in the United Kingdom and vice versa. It is also important to remember that chronic hepatitis can affect mixed breed as well as purebred dogs and that recognition of one cause in a breed does not necessarily

mean that chronic hepatitis in all dogs of that breed are due to the same cause. For example, in many Doberman Pinschers and West Highland White Terriers chronic hepatitis is due to copper accumulation, but in others it is not. In many cases of canine chronic hepatitis, the cause is unknown. This contrasts with the situation in human medicine, wherein most cases of chronic hepatitis are viral and some have defined and often effective treatments that can reverse the disease process. In dogs chronic viral causes have not been convincingly demonstrated, but the histology in some cases is suggestive of this and the search for infectious agents con-



BOX 38-1

# Dog Breeds with a Reported Increased Risk of Chronic Hepatitis\*

Bedlington Terrier (worldwide. Copper storage disease)
Dalmatian (U.S., Copper storage disease)

Labrador Retrievers (worldwide. Copper storage disease in U.S. and Holland. Not copper associated U.K.) females > males

West Highland White Terriers (worldwide. Some copper associated and some not; all countries)

Skye Terriers (reports in U.K. only—may be copper associated. No recent reports)

Doberman Pinschers (worldwide. Some copper storage disease and some not) females > males

American and English Cocker Spaniels (worldwide) males > females

English Springer Spaniels (U.K. and Norway) females > males

<sup>\*</sup> No reported sex ratio unless stated.



BOX 38-2

## Possible Reasons for Breed-related Liver Disease

- Increased susceptibility to infectious causes of chronic hepatitis and/or chronicity of infection
- Mutation in gene involved in metal storage or excretion
- Mutation in gene involved in other metabolic processes (e.g., protease inhibitor production)
- Increased susceptibility to toxic hepatitis (e.g., impaired detoxification of drugs)
- Susceptibility to autoimmune disease

tinues. Most cases therefore remain a nonspecific diagnosis of "chronic hepatitis," and the treatment remains nonspecific and symptomatic. However, in a few notable exceptions, such as copper storage disease and toxic hepatitis, the cause may be known and may be treated specifically. These are outlined in separate sections of this chapter.

#### IDIOPATHIC CHRONIC HEPATITIS

### **Etiology and Pathogenesis**

Idiopathic chronic hepatitis likely represents an unidentified viral, bacterial, or other infection; an unidentified previous toxic event; or, in some cases, autoimmune disease. However, because autoimmune chronic hepatitis has not yet been convincingly demonstrated in dogs, immunosuppressive drugs should not be used or used only very cautiously.

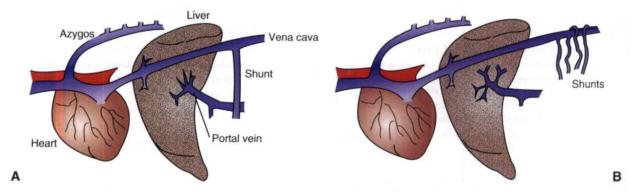
The pathogenesis of chronic hepatitis relates to loss of hepatic mass resulting in loss of function and, late in the disease process, development of portal hypertension. In many cases hepatocyte swelling, fibrosis, and portal hypertension also contribute to cholestasis and jaundice. Ongoing inflammation may also result in bouts of pyrexia and hepatic pain with associated gastrointestinal (GI) and other signs, and many dogs with chronic hepatitis develop negative nitrogen balance and protein-calorie malnutrition. Loss of hepatic function accounts for coagulopathies and adverse drug reactions in affected dogs.

Portal hypertension is an important consequence of chronic hepatitis and fibrosis, and its effects contribute to the clinical signs and death of many affected animals (see also Chapter 39). It causes a typical triad of clinical signs of ascites, GI ulceration, and hepatic encephalopathy (HE). In a healthy dog the pressure in the portal vein is lower than the pressure in the caudal vena cava. However, in association with obstruction and disruption of sinusoids by fibrosis and hepatocyte swelling, portal pressure rises until it exceeds that in the caudal vena cava (portal hypertension). This results in splanchic congestion with splenic congestion, gut wall edema, and eventually ascites. The mechanisms of ascites formation in dogs with liver disease are complex but involve activation of the renin-angiotensin-aldosterone system (RAAS) with sodium retention in the kidneys and increased circulating fluid volume.

If the rise in portal pressure is sustained, multiple acquired PSSs will develop by the opening up of previously nonfunctional vessels; this allows for some of the portal blood to bypass the liver and enter the portal vein directly (Fig. 38-2). These acquired PSSs differ from congenital PSSs in that they are multiple and exist in the presence of increased portal pressure, whereas in patients with congenital PSSs the portal pressure is low. Acquired PSSs lead to HE by a similar mechanism to congenital PSS (see Chapter 39). However, the HE must be medically managed because ligation of acquired PSSs is contraindicated. This is because acquired PSSs are important escape valves to allow dissipation of some of the portal hypertension; therefore any attempt to ligate them will result in fatal splanchic congestion. Acquired PSSs in humans are also recognized to reduce the risk of serious GI ulceration associated with portal hypertension; because of this, they are sometimes created surgically in humans with cirrhosis to reduce the risk of serious bleeds. The same is likely to be true in dogs: GI ulceration is one of the most common causes of death in dogs with chronic hepatitis; acquired PSSs will help reduce this risk.

## **Clinical Features**

Dogs of any age or breed can be affected with idiopathic chronic hepatitis, but there is an increased suspicion in middle-aged dogs of the breeds outlined in Box 38-1. The functional and structural reserve capacity of the liver implies that dogs with chronic hepatitis usually have no clinical signs until late in the disease process, when more than 75% of liver function has gone. By this stage, there is already extensive destruction of liver mass and treatment will be less effective than it would have been earlier in the disease (Fig. 38-3). It is therefore beneficial to diagnose the disease earlier, and dogs with persistently high liver enzyme activities (particularly hepatocellular enzymes such as ALT) should not be



**FIG 38-2**Diagramatic representation of congenital and acquired portosystemic shunts. **A,** Congenital portocaval shunt. **B,** Multiple acquired shunts develop only if the pressure in the portal vein is higher than the pressure in the vena cava.

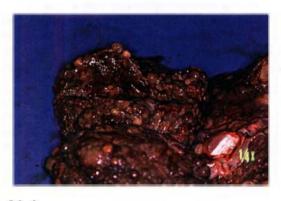


FIG 38-3
Liver from a 6-year-old Bearded Collie that had shown clinical signs for only 1 month before dying from end-stage liver disease. The diagnosis was chronic hepatitis with macronodular cirrhosis and very little normal liver tissue remaining.

ignored. If liver enzyme activities are high for several months and other causes have been ruled out (see the section on secondary hepatopathy), then a liver biopsy should be obtained. This is even more important in breeds at high risk and in those predisposed to treatable diseases, such as copper storage disease.

Once dogs have lost a significant amount of liver mass, they will display clinical signs, but these are typically low-grade, waxing and waning, and nonspecific, making differential diagnosis from other diseases a challenge. Vomiting and diarrhea, anorexia, and polydipsia/polyuria are common. Jaundice and ascites occur in some dogs at presentation and develop later in others, but not in all cases. Ascites at presentation has been identified as a poor prognostic indicator in humans and dogs because it may represent more advanced disease with secondary portal hypertension. HE is uncommon and usually seen only in end-stage disease. The presence of HE strongly suggests the development of acquired PSS. Dogs with chronic hepatitis usually have some degree of protein-calorie malnutrition as a result of chronic hepatic functional impairment and concurrent GI signs. They are

often overtly thin. They may be depressed, but they are also often surprisingly alert considering the severity of their disease.

## **Diagnosis**

Ultimately, a definitive diagnosis requires a liver biopsy, but suspicion of disease is gained from the clinical signs and clinicopathologic features. Clinical signs, clinicopathologic findings, and imaging may be supportive of chronic hepatitis but are not specific. A serum biochemical profile may show a combination of high activities of hepatocellular (alanine transaminase [ALT] and aspartate aminotransferase [AST]) and cholestatic (alkaline phosphatase [ALP] and -glutamyltransferase [GGT]) enzymes, and evidence of decreased parenchymal liver function (low urea, low albumin, and sometimes high bilirubin and bile acid concentrations). Persistent increases in ALT are the most consistent finding in dogs with chronic hepatitis, but they can also be found in other primary and secondary hepatopathies. A high ALP activity is much less specific in dogs, particularly because there is a steroid-induced isoenzyme. Hepatocellular enzymes can become normal in end-stage disease because of a lack of liver mass, but by that stage function tests (e.g., ammonia and bile acid concentrations) will be abnormal, and the dog may even be jaundiced.

Radiographic findings are nonspecific. Dogs with chronic hepatitis often have a small liver (contrasting with cats, in which hepatomegaly is more common), but there is an overlap with normal, and the assessment of liver size is further confused by the variation in gastric axis in deep-chested dogs. If ascites is present, radiographs are not helpful because the fluid obscures all abdominal detail. Ultrasonography is much more useful in assessing hepatic architecture (see Chapter 36). Dogs with chronic hepatitis often have a small, diffusely hyperechoic liver on ultrasonography, although the liver may look ultrasonographically normal in some cases. In other cases it may appear nodular because of macronodular cirrhosis and/or concurrent benign nodular hyperplasia. It is impossible to definitively differentiate benign from malignant nodules on ultrasonographic appear-

ance alone; cytology or biopsy is essential to obtain a definitive diagnosis.

End-stage chronic hepatitis with cirrhosis may appear very similar to noncirrhotic portal hypertension from a diagnostic standpoint, and yet the treatment of the latter is very different and the long-term prognosis much more favorable than with cirrhosis. Therefore a liver biopsy is necessary for a definitive diagnosis and appropriate treatment. It is important to perform a hemostasis profile (one stage prothrombin time; activated partial thromboplastin time, and platelet count) before obtaining a biopsy and to address any coagulopathies or thrombocytopenia before the procedure. Fine needle aspirate (FNA) cytology is of limited value in the diagnosis of chronic hepatitis; the most representative biopsies are wedge biopsies obtained during laparotomy or laparoscopy, although ultrasonographically guided Tru-Cut needle biopsies can be of some benefit.

#### **Treatment**

The aims of treatment of dogs with chronic hepatitis are to treat any identified underlying cause (see subsequent sections), slow progression of the disease if possible, and support liver function and the animal's nutritional and metabolic needs.

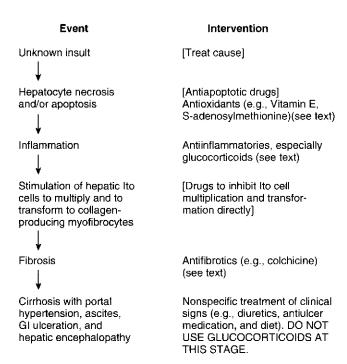
#### Diet

Dietary management is always an important part of treatment in patients with liver disease because the liver is the "first stop" for nutrients on their way from the gut to the systemic circulation and it is intimately involved in the metabolism of nutrients. This metabolism is compromised in patients with liver disease; in addition, dogs with chronic hepatitis typically have protein-calorie malnutrition, so excessive restriction of nutrients can be harmful. The nutritional requirements in dogs with liver disease are outlined in Table 38-2. The most important consideration is dietary protein concentration. It is now recognized in both people and dogs with liver disease that, in order to avoid negative nitrogen balance, dietary protein should not be restricted. However, it is important to feed a high-quality, highly digestible protein to reduce hepatic work and to decrease the amount of undigested protein that reaches the colon, where it is converted to ammonia. Most ammonia reaching the systemic circulation in the portal blood of animals with congenital and acquired PSSs originates not from dietary protein but from enterocyte catabolism of glutamine as their main source of energy. This cannot be avoided without starving the enterocytes, so other means of control of HE are recommended in addition to dietary restriction. Clinical diets available for dogs with liver disease (Hills LD and Royal Canin-Waltham Hepatic support) are ideally formulated, except that they have lower protein than is ideal for a dog with chronic hepatitis. Therefore these diets should be fed as a baseline little and often, with the addition of high-quality protein to the food. Dairy and vegetable protein produce the best results in humans and dogs with liver disease; cottage cheese is a good choice to add to the diet. The amount to add to the food is difficult to estimate. It is advisable to start with 1 or 2 tablespoons of cottage cheese per meal, monitor clinical signs and blood protein levels, and adjust accordingly.

#### Drugs

Drug support in dogs with idiopathic chronic hepatitis is nonspecific and attempts to slow progression of disease and control clinical signs. Specific drug treatments are reserved for patients with an identified underlying cause. Without a biopsy, nonspecific treatment should consist of choleretics, antioxidants, and diet. The use of glucocorticoids must be reserved for biopsy-confirmed cases only.

Glucocorticoids. Glucocorticoids are commonly used in dogs with idiopathic chronic hepatitis, but they should never be used without a biopsy. Biopsies are necessary not only to confirm the presumptive diagnosis but also to rule out any contraindications. There is currently no evidence that idiopathic chronic hepatitis is an autoimmune disease, so glucocorticoids are used in this context for their antiinflammatory and antifibrotic role rather than as immunosuppressives. Fibrous tissue is laid down in the liver by transformed Ito (stellate) cells, and in dogs these are usually stimulated indirectly by cytokines produced by inflammatory cells to transform to collagen-producing cells. The chain of events in idiopathic chronic hepatitis is therefore usually as outlined in Fig. 38-4. Glucocorticoids have an important role to play early in the disease process: Their antiinflammatory effect reduces cytokine formation and Ito



#### FIG 38-4

Chain of events in typical idopathic hepatitis in dogs and points for therapeutic intervention (those in brackets are potential treatments not yet available for clinical use in dogs).



**TABLE 38-2** 

## Dietary Considerations for Dogs with Liver Disease

The diet should be fed little and often (4-6 times a day) and needs to be palatable. A good and sufficient diet is essential for hepatic regeneration and optimal hepatic function.

DIETARY COMPONENT	RECOMMENDATIONS
Protein	Normal amount of high quality (all essential amino acids in optimal amounts), highly digestible (so none left in colon for bacteria to break down to ammonia), and not in excess or requires hepatic metabolism resulting in increased blood ammonia.  Low levels of aromatic amino acids and high levels of branched chain amino acids said to be helpful to reduce hepatic encephalopathy, but evidence is lacking.  Ideal protein to use is dairy or vegetable. Cottage cheese is often used, but it is relatively low in arginine. The easiest way to feed sufficient high-quality protein is to feed a proprietary diet for canine intestinal or liver disease and adjust the protein level to individual's clinical signs. Note diets for canine liver disease have slightly reduced protein content so may need to add more protein e.g., cottage cheese if body weight or blood albumin drops.  Single protein source diet based on dairy or soy protein is recommended after recovery from acute hepatitis.
Fat	No special advice in liver disease. Should not be excessively restricted as an important source of calories and fat maldigestion and steatorrhea because of cholestasis and lack of bile salts very rare. Restrict only if clinical steatorrhea develops. Avoid very high fat diets, particularly with cholestasis or portal hypertension, in which gastrointestinal signs may be exacerbated. Optimizing omega 3: Omega 6 may help reduce inflammation (more research necessary).
Carbohydrate	The carbohydrate used should be highly digestible as a calorie source, reducing need for hepatic gluconeogenesis from fat and protein. Carbohydrate metabolism usually disrupted in hepatic disease. Therefore complex carbohydrates will be better used as an energy source by the animal with liver disease than glucose.
Fiber	Fermentable fiber: may reduce hepatic encephalopathy (conflicting evidence in humans, little evidence in dogs). Broken down to short chain fatty acids in the colon which trap ammonia as ammonium ions. Also beneficial effect on colonic bacteria, increasing nitrogen incorporation into bacteria and reducing ammonia production. (Lactulose is a fermentable fiber).  Nonfermentable fiber: also important because prevents constipation, which is a potential predisposing factor for development of encephalopathy; it increases the contact time for colonic bacteria to act on feces and produce ammonia.  Mixed fiber source in moderate amounts is therefore useful but not too much or it interferes with
Minerals: zinc	the digestion and absorption of nutrients.  Zinc deficiency is common in humans with chronic liver disease. Dogs are proposed to be similar to humans (but little direct evidence exists). Supplementation with zinc proposed to reduce encephalopathy because it is used in metalloenzymes in the urea cycle and in muscle metabolism of ammonia. Zinc is also indicated in copper storage disease because it reduces copper absorption from gut and copper availability in the liver. It may also reduce collagen lay-down in liver and stabilize lysosomal enzymes and also has some antioxidant activity. Supplementing zinc is therefore recommended in any chronic hepatitis in dogs or cats.
Minerals: copper Vitamins: fat soluble	Animals with copper storage disease should be maintained on a low-copper, high-zinc diet.  Vitamin E supplementation may be cytoprotective especially in copper toxicity because of its antioxidant effect.  Vitamin K supplementation may be necessary if clotting times are prolonged, especially if considering biopsies.  Vitamins A and D should not be supplemented. Vitamin A can cause hepatic damage, and
Vitamins: water soluble	vitamin D supplementation can cause calcification in tissues.  B vitamins should be supplemented because there is increased loss in polydipsia/polyuria associated with liver disease. It is recommended that dogs with liver disease receive a double dose of B-vitamins.  Vitamin C should not be supplemented because ascorbate can increase the tissue damage associated with copper and iron in liver disease.

cell stimulation, thus reducing fibrous tissue deposition. They are therefore indicated early in the disease process, when there is inflammation and minimal fibrosis, and once infectious etiologies have been ruled out. In these situations they may slow the progression of the disease (although that has not been proved). The logical dose to use is antiinflammatory (equivalent to 0.5 mg/kg of prednisone and gradually reducing over several weeks by halving the dose and reducing to every-other-day treatment), although immunosuppressive doses also have been used; there is currently insufficient evidence in dogs to advise which is correct.

Glucocorticoids are contraindicated later in the disease, when there is portal hypertension and end-stage fibrosis, or in conditions with noninflammatory fibrosis (e.g., noncirrhotic portal hypertension), in which there is no reason for their use. In these circumstances they are also likely to shorten the life expectancy by increasing the risk of serious GI ulceration (see Fig. 39-1). Hence glucocorticoids should never be used without a histopathologic diagnosis and staging of disease.

Other antiinflammatory or immunosuppressive drugs. Some of the other drugs used in dogs with liver disease also have antiinflammatory activity, particularly zinc, S-adenosylmethionine, and ursodiol (discussed in more detail later). Azathioprine has occasionally been used in dogs with chronic hepatitis, but there is no evidence that it is beneficial; until immune-mediated causes of chronic hepatitis have been proved, it would be wise to avoid the use of this or other potent immunosuppressive medications.

Choleretics. Ursodiol is widely and commonly used in dogs with chronic hepatitis. It is a synthetic hydrophilic bile acid that is choleretic and also modulates the bile acid pool in biliary stasis, making the bile less toxic to hepatocytes. It also has antiinflammatory and antioxidant properties, and recent studies suggest that it is synergistic with S-adenosylmethionine and vitamin E. The only absolute contraindication is complete biliary obstruction, which is very rare in dogs and would usually result in obvious acholic feces. It is logical to use it in any dog with chronic hepatitis, particularly in those associated with biliary stasis, and it can safely be used without a biopsy. However, as with other drugs used in canine liver disease, there is very limited (although encouraging) evidence as to its efficacy. It may be more helpful in some diseases than others, but this is not known yet in dogs. The recommended dose is 10 to 15 mg/kg q12h (or split into two doses given q12h).

Antioxidants. A variety of antioxidants are used in dogs with chronic hepatitis. The most well-documented are vitamin E and S-adenosylmethionine. Vitamin E appears to be beneficial at a dose rate of 400 IU/day for a 30-kg dog given as a water-soluble preparation once a day. Doses for smaller dogs are scaled appropriately. S-Adenosylmethionine is a glutathione precursor and is of particular benefit in dogs with toxic hepatopathy (discussed in more detail later) and those with biliary stasis because bile is a potent oxidant. It is synergistic with Vitamin E and ursodiol, and an argument could be made for it being beneficial in any dog with

chronic hepatitis. The recommended dose is 20 mg/kg PO q24h. There are some studies documenting its use in dogs, but more are needed to define in which diseases it is most useful. S-Adenosylmethionine is a very unstable molecule (because it is a methyl donor) and must therefore be carefully packaged and given on an empty stomach. The pharmokinetics and GI availability in dogs are known for the pure preparation (Denosyl SD4; Nutramax Laboratories), but it is increasingly being marketed as a polypharmacy nutraceutical in preparations with other nutraceuticals and vitamins mixed together. Pharmacokinetic and absorption data should be sought from the manufacturers of these products to ensure that the S-adenosylmethionine is absorbed in effective amounts.

Another antioxidant commonly used in dogs with chronic hepatitis is milk thistle (Silybum marianum). The active ingredients are flavonoids, commonly referred to as silymarin, and the most effective of these is believed to be silybin. There are very few studies of the use of flavonoids in dogs, and the only clinical studies are on acute toxic hepatitis. Silybin undoubtedly has the potential to be a helpful adjunct to therapy in some cases, but much more information on absorption, availability, and ideal dosage is necessary. Silybin is included in many nutraceuticals marketed for dogs with liver disease. One recent study (Filburn et al., 2007) showed that it had very poor absorption alone but was much more bioavailable when complexed with phosphatidylcholine.

Therefore, although antioxidant nutraceuticals have great potential benefits in the treatment of chronic liver disease in dogs and can be safely used without a biopsy, the clinician must be aware of the emerging nature of the information about their bioavailability and efficacy and choose products carefully with this in mind.

Antifibrotics. In inflammatory liver disease and early fibrosis, glucocorticoids have a potent indirect antifibrotic activity by reducing inflammation, as outlined in the preceding sections. Later in the disease process, when there is extensive fibrosis, the direct antifibrotic agent colchicine can be used; there is limited but encouraging anecdotal evidence supporting its effectiveness in dogs. It is an alkaloid derivative that binds tubulin and has the potential to reverse fibrosis. The recommended dose in dogs is 0.03 mg/kg/day PO. Adverse effects are uncommon in dogs but include bone marrow suppression and anorexia/diarrhea; it is the latter that often limits its use in clinical cases.

Antibiotics. There is a primary indication for the use of antibiotics in dogs with ascending biliary tract infections or suspected bacterial infection as a cause of the chronic hepatitis. The latter is rarely proved, but if it is possible that atypical leptospiral infection may be present (e.g., if chronic hepatitis is seen in a dog with access to sources of infection such as rivers or ditches), a course of appropriate antibiotics would be wise to rule this out. The recommended therapy for leptospiral infections is to start with intravenous (IV) amoxicillin at a dose of 22 mg/kg q12h to terminate replication and reduce potentially fatal liver and kidney complications. If leptospiral infection is subsequently confirmed (on

rising titres on serology, dark field microscopy, or PCR of the urine for organisms), this should be followed by doxycycline therapy (5 mg/kg PO q12h for 3 weeks) once liver function is normal to eliminate the chronic renal carrier state. *Bartonella* spp. have occasionally been associated with chronic liver disease in dogs. The optimal treatment for *Bartonella* spp. in dogs has not been established. Macrolides (e.g., erythromycin) or alternatively fluoroquinolones or doxycycline have been shown to have some efficacy against some *Bartonella* spp. in dogs. It has been suggested that 4 to 6 weeks of treatment might be necessary to eliminate infection.

Antibiotics are also used as part of supportive treatment in dogs with HE caused by acquired PSS in end-stage chronic hepatitis, in a similar way to dogs with congenital PSS to reduce toxin absorption from the gut and the risk of systemic infections (see Chapter 39). Ampicillin is often used long term in these cases at a dose of 10 to 20 mg/kg, PO or IV q8-12h.

As with other drugs, the clinician should avoid any antibiotics that increase hepatic work or the risk of hepatotoxicity. Thus tetracyclines, potentiated sulphonamides, nitrofurantoin, and erythromycin should be avoided unless necessary (e.g., with confirmed leptospirosis or bartonellosis) because they are potentially hepatotoxic.

### COPPER STORAGE DISEASE

### Pathogenesis and Etiology

Copper storage disease has been recognized as a cause of acute and chronic hepatitis in several breeds, the best researched of which is the Bedlington Terrier (see Box 38-1). Other breeds in which copper storage disease has been reported are Dalmatians (in the United States and Canada), Labrador Retrievers (in the United States and Holland), and some Doberman Pinschers (in Holland), although individual members of all these breeds have also been reported with chronic hepatitis without copper accumulation. In addition, copper storage disease has been suspected but not extensively investigated in West Highland White Terriers and Skye Terriers. It is also possible for seemingly normal dogs without a recognized copper storage disease to develop copper-associated chronic hepatitis if fed a diet very high in copper, such as dry calf feed (Van den Ingh et al., 2007).

Copper is excreted in the bile and can build up as a secondary phenomenon in any type of chronic hepatitis associated with cholestasis. In these cases the accumulation is usually mild, often in zone 1 (peribiliary), and the amount of copper does not correlate with the severity of the disease. It is unclear whether copper chelation is helpful in dogs with secondary copper build-up, but probably it is not. The peribiliary distribution and lack of correlation between amount of copper build up and clinical signs helps to distinguish these cases from "true" copper storage disease, in which the copper accumulation is the cause rather than an epiphenomenon of the disease and accumulation is usually marked, progressive, correlated with disease severity, and in

Zone 3 (perivenous; see Fig. 35-4 for an explanation of hepatic zonation).

True copper storage disease likely represents a genetic defect in copper transport and/or storage, but the only breed in which this has been defined is the Bedlington Terrier. In this breed it is inherited as an autosomal recessive trait, and up to 60% of Bedlington Terriers in some countries have been affected in the past, although the prevalence is now decreasing as a result of selective breeding. The disease is confined to the liver, and there appears to be a specific defect in hepatic biliary copper excretion (probably in transport from the hepatocyte lysosomes to the biliary tract). Recent work has identified at least one genetic defect associated with the disease: a deletion in the MURR1 gene (now COMMD1; Van de Sluis et al., 2002), which codes for a protein of unknown function. However, Bedlington Terriers with copper storage disease but without a COMMD1 deletion are now being reported in the United States, United Kingdom, and Australia (Coronado et al., 2003; Heywood, 2006; Hyun et al., 2004), suggesting that there is at least one other mutation involved in the breed that has yet to be identified.

#### **Clinical Features**

Affected Bedlington Terriers can present with either acute or chronic clinical signs, depending on individual factors, such as the amount of copper in the diet, and also likely other factors, including concurrent stress and disease. If there is rapid and marked build-up, dogs may present with acute fulminant hepatic necrosis and no previous clinical signs. This is usually seen in young to middle-aged dogs and is often accompanied by acute hemolytic anemia caused by the rapid release of copper into the circulation. The prognosis is poor, and most animals die within a few days. Fortunately, this is uncommon; most dogs have a more chronic, protracted course with several years of copper build-up and persistently high ALT activity, culminating in the development of chronic hepatitis with piecemeal necrosis, inflammation, and bridging fibrosis. Clinical signs are therefore recognized in these individuals only late in the disease process and are usually those of canine chronic hepatitis. These dogs usually present at about 4 years old but may be younger (Fig. 38-5). Eventually, if not treated, affected dogs will develop cirrhosis.

The clinical signs and progression in other breeds with copper storage disease are similar to those in Bedlington Terriers. The disease in Dalmatians is associated with acute onset, rapid progression, and very high levels of hepatic copper in the absence of significant clinical, clinicopathological, or histological evidence of cholestasis. Affected dogs usually present as young adults with acute onset of GI signs and polydipsia/polyuria, by which time severe liver disease is already present. Labrador Retrievers with copper storage disease have an average age at presentation of 7 to 9 years (range, 2.5 to 14 years). The clinical signs are relatively mild and included anorexia, vomiting, and lethargy. Doberman Pinschers appear to have a long phase of subclinical disease culminating, in untreated cases, in an acute-on-chronic

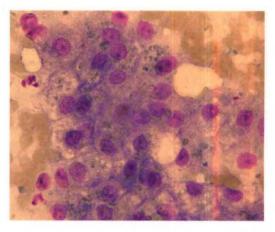


FIG 38-5
Beddlington Terrier with copper storage disease. (From Hall EJ, Simpson JW, Williams DA, editors: BSAVA manual of canine and feline gastroenterology, ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

disease and rapidly progressive deterioration. However, it is unclear how many of the clinically affected Doberman Pinschers described in the literature had copper storage disease and how many had idiopathic chronic hepatitis, so the true presenting signs of copper storage disease in this breed are unclear. Most published studies on true copper storage disease in Doberman Pinschers describe diagnosis and treatment of subclinical disease.

### **Diagnosis**

The magnitude of increase in liver enzyme activities and the diagnostic imaging findings in dogs with chronic copper storage disease are very similar to those of dogs with idiopathic chronic hepatitis. Therefore a definitive diagnosis requires a liver biopsy and estimation of the copper concentration in the liver. This can be done qualitatively on formalin fixed sections using rhodanine staining to detect copper; correlations between quantitative and qualitative estimation of copper accumulation have been published (Shih et al., 2007). The finding of large accumulations of copper in hepatocytes on cytology with rubeanic acid is also very suggestive of copper storage disease (Fig. 38-6; Teske et al., 1992). Quantitative measurement of copper content can also be performed, but this requires a large biopsy specimen carefully taken and stored in copper-free tubes. In addition to estimating copper content, the liver biopsy will give an indication of the chronicity and extent of liver damage, which will affect treatment decisions in a very similar way to chronic hepatitis. Bedlington Terriers can be tested for the COMMD1 deletion either before breeding or when newly acquired to assess their risk for this disease, but an absence of the COMMD1 deletion does not guarantee that the dog will not be affected. The genetic test is currently offered via mouth swabs at the Animal Health Trust in Newmarket, U.K. (details at http://www.aht.org.uk/sci\_diag\_disc\_genetic\_main.htm) and by Vet Gen in the United States (www.vetgen.com). To rule out copper storage disease through a liver biopsy in a



Cytology of hepatocytes from Bedlington terrier with copper storage disease demonstrating copper granules (rubeanic acid stain). (Courtesy Elizabeth Villiers; from Hall EJ, Simpson JW, Williams DA, editors: BSAVA manual of canine and feline gastroenterology, ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

breeding animal, clinicians should obtain a biopsy when the dog is about 12 months old, by which time there will be sufficient copper build-up to diagnose the disease. In much older animals, cirrhosis with nodular regeneration can develop, and the nodules will have a lower copper content than the rest of the liver, confusing diagnosis if a regenerative nodule is inadvertently biopsied.

#### **Treatment**

The ideal treatment in a dog known to be affected is prevention. Bedlington Terriers with the COMMD1 mutation should be fed a low-copper, high-zinc diet. The proprietary liver diets formulated for dogs (Royal-Canin Hepatic support or Hills canine LD) have low copper and high zinc concentrations but are also moderately protein restricted, so it would be wise to supplement with a low-copper protein source (e.g., cottage cheese) in growing dogs. It is also important to avoid giving the dog tap water from copper pipes in soft water areas; bottled water should be used instead. Box 38-3 gives a list of common high-copper foods that should be avoided and high-zinc foods that could be supplemented.

Dogs that present with an acute crisis should be treated with intensive support in exactly the same way as dogs with acute hepatitis (Box 38-4). Blood transfusion may be necessary if hemolysis is severe. Copper chelation is unlikely to be beneficial acutely, but chelation with 2,2,2-tetramine (trientine) could be considered (or 2,3,2-tetramine if obtainable) because this can chelate rapidly. Trientine is available as a drug licensed for humans (Syprine,® Merck Sharp and Dohme). The recommended dose in dogs is 10 to 15 mg/kg PO q12h 30 minutes before a meal. 2,3,2-Tetramine is difficult to obtain. Penicillamine is *not* helpful in an acute crisis because chelation takes weeks to months. However, it should be noted that there is much less information available about



BOX 38-3

Foods Rich in Copper and Zinc

#### Copper

- \*Shellfish
- \*Liver
- Kidney, heart
- Cereals
- Cocoa
- Legumes
- Soft tap water (copper pipes)

#### Zinc

- Red meat
- Egg yolks
- Milk
- Beans, peas
- Liver
- Whole grains, lentils
- Rice
- Potatoes

the pharmacokinetics, drug interactions, and toxicity of trientine in dogs than there is for D-penicillamine. Reported adverse effects include nausea, gastritis, abdominal pain, melena, and weakness. On recovery, the animal should continue on long-term treatment, as outlined in the following sections.

Treatment of dogs that already have high hepatic copper concentrations documented by biopsy but are not in an acute crisis consists of active copper chelation, zinc supplementation, and use of a low-copper diet and additional supportive therapy. The chronic hepatitis secondary to copper storage disease should be treated the same way as in dogs with idiopathic chronic hepatitis, using antioxidants, ursodiol, and other supportive medication (see the section on chronic idiopathic hepatitis). There is a particular role for antioxidants such as vitamin E and S-adenosylmethionine in metal-induced liver injury. Chelation can be achieved using either D-penicillamine or trientine. D-penicillamine takes months to have a significant effect on the copper content of the liver but is easily available and its pharmacokinetics and toxicity in dogs are well documented. The recommended dose is 10 to 15 mg/kg PO q12h 30 minutes before meals. It also has weak antifibrotic and antiinflammatory properties. Starting at the lower end of the dose range and increasing the dose after 1 week (or dividing the dose and giving it more frequently) can reduce the common adverse effects of vomiting and anorexia. It has also been reported to cause nephrotic syndrome, leukopenia, and thrombocytopenia in dogs, so a complete blood count and urine samples should be monitored regularly during therapy. A decrease in liver copper content of about 900 µg/g dry weight per year can be anticipated in dogs treated with D-penicillamine. Trientine (2,2,2 tetramine) is another efficacious copper chelator that



# Outline of Treatment Recommendations for Acute Fulminant Hepatitis

- Identify and treat cause if possible (e.g., remove drugs implicated; treat leptospirosis; give N-acetylcysteine (150 mg/kg by IV infusion in 200 ml 5% glucose over 15 minutes, followed by 50 mg/kg IV infusion in 500 ml over 4 hours then 100 mg/kg IV infusion in 1000 ml over 16 hours) +/- cimetidine (5-10 mg/kg IV, IM or PO tid) for acetaminophen toxicity).
- Fluids: Careful IV fluid therapy: dextrose saline with added potassium often most appropriate. Measure blood glucose and electrolyte concentrations every few hours and adjust appropriately. Use peripheral catheter and monitor renal function (use central catheters only when confirmed that there is no coagulopathy or high risk of unnoticed bleeding around catheter). Monitor carefully: Ensure adequate urine output and reversal of dehydration, but do not overinfuse or worsen fluid retention.
- Treat coagulopathy as necessary: Consider fresh frozen plasma and vitamin K.
- Treat acute hepatic encephalopathy: Consider propofol infusions and lactulose/neomycin enemas. Regularly monitor blood glucose and potassium, and supplement as necessary.
- Treat any gastrointestinal ulceration: Consider acid secretory inhibitors (ranitidine or omeprazole).
- Treat any ascites with spironolactone +/- furosemide (see Chapter 39).
- Consider antibiotics in all cases to protect against infectious complications, particularly septicemia of gut origin.
   Certainly give antibiotics to all pyrexic cases intravenously. Use broad-spectrum agents that are safe in liver disease.
- Food: Nothing by mouth for first 1 to 3 days; then feed diet based on dairy or soy protein: high quality protein, not restricted.

may be used and can remove copper from the liver more rapidly than D-penicillamine. Details of dose and potential adverse effects are given in a preceding section.

Copper chelation treatment is continued until normal liver copper concentration is reached; this is best determined by liver biopsy and copper quantification or cytologic estimate. Treatment should then be stopped to prevent copper deficiency, which can occur after prolonged, overzealous copper chelation and can result in severe effects of copper deficiency with weight loss and hematemesis. The regimen can then be changed to a preventive protocol consisting of a copper-restricted diet and zinc administration.

# INFECTIOUS CAUSES OF CANINE CHRONIC HEPATITIS

Primary chronic hepatitis caused by infectious agents is uncommon in dogs, although there may be a yet unidenti-

particularly high in copper

fied infectious cause in some dogs with what appears to be idiopathic chronic hepatitis. Clinicians should keep this possibility in mind before prescribing immunosuppressive medication.

To date, there has been no convincing demonstration of a viral cause of canine chronic hepatis, although it has been suspected in several cases. The most common viral cause of chronic hepatitis in people is hepatitis B virus, a hepadnavirus. Similar hepadnaviruses associated with hepatitis have been identified in woodchucks, ground squirrels, tree squirrels, and ducks, but attempts to identify hepadnaviruses by PCR in the liver of dogs with chronic hepatitis or hepatocellular carcinoma have failed. Two other viruses have been suggested as a possible cause of canine chronic hepatitis: canine adenovirus type 1 (CAV1) and canine acidophil cell hepatitis virus. CAV1 causes acute fulminant hepatitis in immunologically naive dogs, but it can also cause chronic hepatitis experimentally in partially immune dogs. However, its importance in naturally occurring chronic hepatitis is unclear, and studies are conflicting. An alternative viral cause of canine acute, persistent, and chronic hepatitis was proposed in Glasgow by Jarrett et al. in 1985 and named canine acidophil cell hepatitis virus pending isolation and identification. The virus appeared to be transmissible by subcutaneous injection of liver homogenate and serum and was apparently capable of producing a chronic hepatitis marked by fibrosis and hepatocyte necrosis, but sparse inflammatory changes (Jarrett et al., 1985, 1987). It was proposed at the time that this was the most important cause of hepatitis in Glasgow. However, there have been no further published studies by either these or other workers regarding the identity or significance of this virus, so its identity and role remain unknown.

Bacterial infections have been sporadically reported as a cause of canine chronic hepatitis, but their importance is unclear. Bile-tolerant *Helicobacter* spp. can cause hepatitis centered on the bile ducts in rodents; there is one report of necrotizing hepatitis associated with *Helicobacter canis* infection in a pup (Fox et al., 1996). However, no further work has been reported in dogs, and a clear association between *Helicobacter* infection and liver disease has yet to be demonstrated.

Infections with apparently atypical leptospires may be a clinically relevant and underestimated cause of chronic hepatitis in dogs. Most dogs in the United States are vaccinated regularly against *Leptospira interrogans* serovars *canicola* and *icterohaemorrhagiae*, so it is assumed that leptospiral infection is now a rare disease. However, recent studies have shown an emergence of diseases associated with other serovars; in addition, there is little immunologic cross-reaction with the vaccine serovars. Infection with "atypical" leptospires, particularly *L. grippotyphosa*, can cause a chronic hepatitis with ascites, particularly in young dogs; azotemia is uncommon in these dogs. Histologically, the liver of dogs with confirmed atypical leptospire infection has portal and intralobular inflammation (i.e., mainly lymphocytic-plasmacytic with some neutrophils and macrophages). There

may also be periportal and portoportal fibrosis that may disrupt the hepatic architecture. The organisms are sparse and difficult to find with conventional staining techniques, so it is very possible that some cases of leptospiral hepatitis are misdiagnosed as immune-mediated disease on the basis of the histological appearance. There is also often a poor serological response in affected dogs, further complicating diagnosis.

Adamus et al. (1997) noted the similarity in age bias (6 to 9 months) and histological appearance between leptospiral hepatitis and lobular dissecting hepatitis, and it has been suggested that undiagnosed infections may be a cause of lobular dissecting hepatitis in some young dogs (discussed in more detail later). There have also been recent sporadic reports of *Bartonella henselae* and *Bartonella clarridgeiae* in dogs with chronic liver disease, but again their significance as a cause of the disease is unclear. Peliosis hepatis, rather than chronic hepatitis, is the more classical histological appearance associated with *Bartonella* spp. infection in humans and has been reported in one dog (Kitchell et al., 2000). Serology or PCR for *Bartonella* spp. is available.

A recent study (Boomkens et al., 2005) evaluated 98 liver samples from dogs with chronic hepatitis using nested PCR for Hepadnaviridae, *Helicobacter* spp., *Leptospira* spp., *Borrelia* spp., hepatitis A virus, hepatitis C virus, hepatitis E virus, canine adenovirus, and canine parvovirus and failed to find evidence of infection in any of the dogs. More work is needed before potential infectious causes of chronic hepatitis in dogs can be completely ruled out.

#### LOBULAR DISSECTING HEPATITIS

Lobular dissecting hepatitis is an idiopathic inflammatory disorder recognized predominantly in young dogs; it has a typical histological appearance of fibrotic dissection of lobular parenchyma into individual and small groups of hepatocytes. It has been reported in several breeds, including families of Standard Poodles and Finnish Spitzes. It has been proposed that lobular dissecting hepatitis does not represent a distinctive disease but rather a response of the juvenile liver to a variety of insults. Infectious etiologies have been suggested, although not proved, and the age of onset and histological appearance bear a striking resemblance to atypical leptospiral infection in dogs. Treatment recommendations are similar to those for canine chronic hepatitis (see preceding section).

### TOXIC CAUSES OF CHRONIC HEPATITIS

Toxins and drug reactions more commonly cause acute, necrotizing hepatitis than chronic disease. Phenobarbital or primidone can cause either acute or chronic hepatotoxicity (see later discussion). Lomustine (CCNU) can also cause delayed, cumulative dose-related, chronic hepatotoxicity that is irreversible and can be fatal. Another occasional reported cause of chronic liver damage is phenylbutazone. Most other reported hepatotoxic drugs and toxins cause an acute hepatitis (see section on acute hepatitis and Box 38-5). Certain mycotoxins, including aflatoxins, can cause acute or



### Potential Causes of Acute Fulminant Hepatitis in Dogs

#### Infections

- Canine adenovirus type 1
- Neonatal canine herpes virus
- Leptospira interrogans (various serovars)
- Endotoxemia

#### Thermal

Heat stroke

#### Metabolic

 Acute necrosis associated with copper storage disease in Bedlingtons, Dalmatians, and some Labradors and Dobermans (see Box 38-1)

#### Toxic or Drug-induced

- Acetaminophen
- Phenobarbital or primidone
- Carprofen (especially Labrador Retrievers)
- Mebendazole
- Thiacetarsamide
- Mercury
- Potentiated sulphonamides
- Mebendazole
- Xylitol
- Aflatoxin
- Nitrofurantoin
- Lomustine (CCNU)

chronic liver disease in dogs depending on the dose ingested and period of exposure. Dogs scavenge and eat contaminated food more often than humans do, so it is possible that a number of cases of canine chronic hepatitis are due to acute or chronic ingestion of unidentified toxins. Because a wide variety of drugs have been reported as causing hepatic adverse reactions in humans and dogs, a drug reaction should be considered in any dog with chronic hepatitis that is also on long-term therapy of any sort, although care should be taken not to overdiagnose drug reactions; chronic hepatitis should be considered as possibly drug related only when there is a clear temporal relationship with drug intake and likely alternative causes have been excluded.

### **ACUTE HEPATITIS**

### **Etiology and Pathogenesis**

Acute hepatitis is much less common than chronic hepatitis in dogs but, when severe, carries a much poorer prognosis. Treatment focuses on providing supportive measures and allowing the liver to recover. Dogs with acute hepatitis are at high risk of disseminated intravascular coagulation (DIC). Severe loss of liver function is also fatal because it cannot be replaced artificially while awaiting recovery; there is no such

thing as liver dialysis. However, because of the remarkable regenerative capacity of the liver, animals that recover from the acute phase of the disease can recover completely, with no permanent hepatic injury, as long as they are fed and supported properly.

Most causes of acute fulminating hepatitis in dogs are infectious or toxic (see Box 38-5). In unvaccinated dogs CAV-1 and leptospira are important differential diagnoses. Dogs with copper storage disease can present acutely and often will have hemolysis associated with high serum copper concentration, in addition to acute hepatic necrosis. Xvlitol, an artificial sweetener, has recently been reported to cause acute hepatic necrosis in dogs (Dunayer et al., 2006) with a high mortality. Aflatoxin in contaminated feed-stuffs also recently caused acute and subacute hepatitis with a high mortality in dogs (Newman et al., 2007). The most common drugs implicated in causing acute hepatic necrosis in dogs are listed in Box 38-5, but potentially any drug could cause idiosyncratic hepatic necrosis in an individual dog. Recently, a case of destructive cholangitis ("disappearing bile duct syndrome") was reported in a dog as a suspected drug reaction to either one or a combination of amoxicillinclavulanate, amitraz and milbemycin oxime (Gabriel et al., 2006), and we have seen this in a clinical case likely caused by an indiosyncratic reaction to amoxicillin-clavulanate.

### **Clinical Features**

The clinical features of acute fulminating hepatitis, independent of the cause, relate to the acute loss of hepatic function together with the effects of generalized cell necrosis and release of inflammatory cytokines and tissue factors. Dogs usually present with acute onset of one or more of the following: anorexia; vomiting; polydipsia; dehydration; hepatic encephalopathy with depression progressing to seizures and/or coma; jaundice; fever; cranial abdominal pain; coagulopathy with petechiae and possible hematemesis and melena; and, in some cases, ascites and splenomegaly resulting from acute portal hypertension. Renal failure is a severe complication in some cases with both prerenal and intrinsic renal components. In humans with acute hepatic failure, hypotension, cardiac arrhythmias, cerebral and pulmonary edema, and pancreatic inflammation also have been reported; these may occur in some dogs, although they have not been specifically reported.

### Diagnosis

Diagnosis is usually made on the basis of history, clinical signs, and clinicopathologic findings. Liver histopathology should be confirmatory, but results are often not obtained until recovery (or postmortem) because of the severe acute nature of the disease. A history of recent drug or toxin exposure is important in implicating these as a cause; vaccination status is an important consideration for infectious causes.

On clinical pathology dogs with acute hepatitis often have early, marked increases in hepatocellular enzyme ALT and AST activities (tenfold to >100-fold). Jaundice and increases in markers of cholestasis may also occur; the rare cases of

destructive cholangitis are characterized by early, severe jaundice and marked increases in ALP activity and hyperbilirubinemia. Hypoglycemia and hypokalemia are common in dogs with acute hepatitis, and azotemia is seen in some cases, as a result of both prerenal and renal causes. Hemostatic abnormalities, with both prolonged clotting times and thrombocytopenia, are frequently present and can be a sign of developing DIC (see Chapter 87). Diagnostic imaging is not usually very helpful in dogs with acute hepatitis. There may be hepatomegaly and a diffuse change in hepatic echogenicity; in some cases there may be splenic congestion and/ or ascites, but these changes are not specific and do not help define the cause or extent of the damage. In some patients the ultrasonographic exam is unremarkable.

### Treatment and Prognosis

Treatment of acute fulminant hepatitis in dogs is largely supportive and is outlined in Box 38-4. Every attempt should be made to identify and treat the primary cause at the same time that supportive therapy is instituted. Corticosteroid treatment is not indicated in these cases and may in fact worsen the prognosis by increasing the risk of GI ulceration and thrombosis. The owner should be warned of the poor prognosis for recovery in spite of intensive support, and in severe cases, early referral to an intensive care unit should be considered. However, dogs that recover from the acute phase have a good chance of complete recovery. Some research in humans and animals has suggested that chronic liver lesions are less likely to develop if a single-protein milk or soybean-based diet is fed in the recovery phase.

### **BILIARY TRACT DISORDERS**

Biliary tract disorders are less common in dogs than in cats, but both primary biliary tract disorders and extrahepatic bile duct obstruction are recognized in dogs. In addition, destructive cholangitis caused by drug reactions leading to severe cholestasis and icterus has been recognized occasionally in dogs (but not cats). Dogs occasionally develop congenital hepatic and renal cysts, similar to Caroli's disease in humans.

### **CHOLANGITIS AND CHOLECYSTITIS**

As discussed in the preceding section, primary biliary tract disease is less common in dogs than in cats. The clinical signs and diagnostic evaluation are very similar to those in cats with neutrophilic cholangitis (see Chapter 37). Dogs can be of any age or breed, and the typical presentation is acute onset of anorexia, jaundice, and vomiting, with or without pyrexia. In some cases there may have been a previous history of acute enteritis or pancreatitis, suggesting a potential cause for ascending biliary infection from the gut. Mechanical obstruction and gallbladder mucocele (discussed in more detail later) should be ruled out first, usually by ultrasonography, and then liver and bile and/or gallbladder mucosa specimens should be obtained for histopathology and micro-

bial culture and sensitivity testing, preferably before antibiotic treatment is initiated.

Liver biopsies and bile samples can be obtained by direct visualisation during surgery or laparoscopy or via ultrasonographic guidance. The latter method carries a greater risk of bile leakage; to minimize this, a 22-gauge needle attached to a 12-ml syringe is used for cholecystocentesis (bile retrieval), and an attempt is made to evacuate the gallbladder. The procedure is best performed under general anesthesia rather than heavy sedation to minimize the chance of patient motion during aspiration. The risk of iatrogenic bile or septic peritonitis is greatest with patients with a severely diseased gallbladder wall (determined ultrasonographically); surgical treatment is necessary if bile peritonitis occurs. Enteric organisms similar to those found in cats are most commonly found, and the most common isolate in several studies is Escherichia coli. Other organisms reported are all of gut origin and include Enterococcus sp., Klebsiella sp., Clostridium sp. (which may be a gas-forming species causing emphysematous changes in the gallbladder wall visible radiographically), fecal Streptococcus sp., Corynbacterium spp., and Bacteroides sp. Antibiotic resistance is relatively common among isolates and can also develop during therapy, underscoring the importance of obtaining bile samples for culture and sensitivity whenever possible. Choleliths can be found in association with cholecystitis or cholangitis; the cause-and-effect relationship is not always clear.

#### **GALLBLADDER MUCOCELE**

Gallbladder mucocele has recently been reported as a common cause of clinical signs of biliary tract disease in dogs (Figure 38-7). The cause is unclear, but it is most common in middle-aged to older dogs; there appears to be a breed predisposition in Shetland Sheepdogs in the United States (Aguirre et al., 2007). Other suggested breed associations are Cocker Spaniels and Miniature Schauzers. It has been proposed that sterile or septic inflammation of the gallbladder wall and/or disordered gallbladder motility predispose to mucocele formation. In the Shetland Sheepdogs there appeared to be an association between gallbladder mucocele and dyslipidemias, usually caused by other concurrent diseases such as pancreatitis, hyperadrenocorticism, hypothyroidism, and diabetes mellitus.

Clinical signs vary. In some dogs mucocele is clinically silent and is an incidental finding on abdominal ultrasonography (Fig. 38-7). In others nonspecific clinical signs are seen similar to those of other biliary tract diseases with anorexia, lethargy, vomiting, and icterus. Some dogs present acutely because of gallbladder rupture and bile peritonitis.

Treatment is usually surgical for clinically affected dogs with cholecystectomy with or without biliary diversion. There is a high perioperative mortality, particularly for dogs that have biliary diversion surgery. However, those that survive the perioperative period have a good long-term prognosis. Medical management of subclinical mucoceles has been reported in Shetland Sheepdogs (Aguirre et al., 2007). This consisted of a low-fat diet (such as Hills ID or



FIG 38-7

**A,** Ultrasonographic transverse image of the gallbladder of a dog with a mucocele; note the stellate pattern to the bile. The mucinous material does not move with change in patient position. **B,** Appearance of the gallbladder and contents after surgical removal. (Courtesy Dr. Kathy A. Spaulding, North Carolina State University, College of Veterinary Medicine.)



FIG 38-8

**A,** Jaundiced ocular and **B,** oral mucous membranes in a 6-year-old English Springer Spaniel with extrahepatic biliary obstruction caused by acute-on-chronic pancreatitis. The jaundice resolved uneventfully with medical management.

Royal-Canin Waltham intestinal low fat or Eukanuba intestinal diets) with a choleretic (ursodeoxycholic acid 10-15 mg/kg total dose daily, preferably split twice daily) and an anti-oxidant (S-adenosylmethionine 20 mg/kg PO q24h). In one dog this resulted in resolution of the mucocele, in two dogs the mucocele remained static, one dog died as a result of gallbladder rupture, and one dog died as a result of pulmonary thromboembolism, both within 2 weeks of diagnosis; two dogs were lost to follow-up. It would seem sensible also to address the underlying cause of the dyslipidemia in all cases, whether surgically or medically managed.

# EXTRAHEPATIC BILE DUCT OBSTRUCTION

The causes of extrahepatic bile duct obstruction (EBDO) in dogs are very similar to those in cats (see Box 37-4) with the exception of liver flukes, which are uncommon in dogs.

The most common cause of EBDO in dogs is extraluminal obstruction from acute-on-chronic pancreatitis (see Chapter 40), but intestinal foreign bodies, neoplasia, bile duct involvement in a diaphragmatic hernia, and other processes can also cause EBDO (Fig. 38-8). Bile duct injuries that heal and result in stricture formation several weeks later are also seen in dogs; the common bile duct (CBD) may be compressed when carried with the liver into the thorax in dogs with diaphragmatic hernia. Extraluminal compressive lesions, such as pancreatic, biliary, or duodenal neoplasms, are less common causes, and cholelithiasis as a cause of EBDO is rare. To be considered EBDO, a pathologic process must exist at the level of the CBD that impedes bile flow into the duodenum. Only if bile flow has been completely interrupted for several weeks do acholic feces, vitamin K-responsive coagulopathy, and repeated absence of urobilinogen in properly processed urine specimens occur. If obstruction is incomplete, these features are not present and the constellation of signs and clinicopathologic test results resembles those of other, nonobstructive biliary tract disorders.

#### **BILE PERITONITIS**

Bile peritonitis results most often from abdominal trauma damaging the common bile duct (e.g., penetrating injury, horse kick, automobile accident) or pathologic rupture of a severely diseased gallbladder, which sometimes occurs after diagnostic ultrasonography-guided aspiration. Early signs of bile peritonitis are nonspecific, but with progression, jaundice, fever, and abdominal effusion are seen. When bile, which is normally sterile, comes in contact with the peritoneal surface, resultant cell necrosis and changes in permeability predispose to infection with bacteria that move across the intestinal wall. Hypovolemia and sepsis may occur in animals with undetected bile peritonitis.

### **Clinical Features**

Presenting clinical signs and clinicopathologic and physical examination findings of all these disorders may not differ greatly unless the underlying condition has caused EBDO or bile peritonitis. Regardless of the underlying disorder, typical clinical signs are jaundice, acute or chronic vomiting, anorexia, depression, weight loss, and occasionally vague cranial abdominal pain. Because of the protected location of the gallbladder in the abdomen, it is rarely possible to be able to palpate it in a dog with EBDO, unless the gallbladder is greatly enlarged.

### **Diagnosis**

The pattern of clinicopathologic findings typical of biliary tract disorders is that of hyperbilirubinemia, high serum AP and GGT activities, high fasting and postprandial serum bile acid (SBA) concentrations, and less severe changes in serum ALT activity. SBA concentrations increase early in dogs with biliary stasis; in these circumstances the degree of SBA elevation gives no indication of liver function. Generally, more severe cholestatic lesions are associated with more severe clinicopathologic changes. Fractionating the total bilirubin concentration into direct- and indirect-reacting components (i.e., the van den Bergh reaction) does not distinguish intrahepatic from extrahepatic cholestasis or obstructive from nonobstructive cholestasis. Radiographically, there may be evidence of hepatomegaly and a mass effect in the area of the gallbladder on survey abdominal films. Gas shadows associated with the gallbladder and other biliary tract structures could be ascribed to ascending infection with gas-forming organisms. Findings consistent with acute-onchronic pancreatitis as an underlying cause of EBDO are loss of serosal detail in the area of the pancreas as an indication of localized peritonitis, trapped pockets of gas in the duodenum, and duodenal displacement. However, in many cases of chronic pancreatitis imaging findings may be less severe or normal in spite of extensive fibrosis around the bile duct. Choleliths form in dogs in a manner similar to the way they form in cats, usually as a sequela to cholestasis and infection, but they may also be found in asymptomatic dogs. These concretions are radiolucent unless they contain calcium, which occurs about 50% of the time. Inflammatory abdominal effusion is expected in dogs with bile peritonitis but not in those with most causes of EBDO (except for effusions associated with pancreatitis or pancreatic cancer).

The ability to differentiate medical from surgical causes of jaundice has been refined with the development of ultrasonography, although this imaging modality is certainly not foolproof. Dilated and tortuous hepatic bile ducts and CBD, as well as gallbladder distention, are convincing ultrasonographic evidence of EBDO at the CBD or sphincter of Oddi. When dilated biliary structures are seen, it might be difficult to distinguish EBDO that requires surgical intervention from resolving, transient EBDO associated with severe acute-onchronic pancreatitis or from nonobstructive biliary disease (e.g., bacterial cholecystitis/cholangitis) unless a source of obstruction is specifically identified (e.g., pancreatic mass, cholelith in the CBD). Prolonged fasting causes gallbladder enlargement because of delayed evacuation and should not be overinterpreted. In addition, cystic hyperplasia and epithelial polyp formation are common lesions in older dogs, not to be confused with choleliths in the gallbladder. A stellate appearance to the contents of the gallbladder is characteristic of gallbladder mucocele. Monitoring the serum bilirubin concentration to determine when to intervene surgically is not worthwhile because it begins to decline over days to weeks, without relief of obstruction, in both cats and dogs with experimentally induced EBDO. Conversely, in some dogs a significant proportion of bilirubin becomes irreversibly bound to albumin in the circulation ("biliprotein"), resulting in delayed clearance and continued elevation of serum bilirubin concentration for up to 2 weeks after the initial insult has resolved.

### **Treatment and Prognosis**

If the distinction between medical and surgical causes of jaundice is not clear, it is safer to proceed surgically to avoid excessive delays in diagnosis. Surgery is required in dogs with persistent EBDO, bile peritonitis, and gallbladder mucocele. As with any other form of liver disease, it is important to stabilize the patient with fluids and electrolytes and perform a hemostasis profile and platelet count before surgery. Prolonged coagulation times may respond to vitamin K injections (1 mg/kg SQ q24h for 24 to 48 hours before and after surgery), but if not, a plasma transfusion is advisable before surgery to replace clotting factors. If surgery for bile peritonitis is to be delayed, peritoneal drainage should be established to remove noxious, bile-containing abdominal fluid and for lavage. Should a site of obstruction or biliary injury not be identified, at least tissue (i.e., liver, gallbladder mucosa) and bile specimens can be obtained for histopathologic and cytologic evaluation and bacterial culture and sensitivity testing. Any abdominal fluid should be analyzed cytologically and cultured for aerobic and anaerobic bacteria. A liver biopsy specimen should also be obtained in all cases. Typical hepatic histopathologic findings in dogs with early EBDO

are canalicular bile plugs and bile ductular proliferation, with degrees of periportal inflammation and fibrosis in chronic cases. Confounding biliary infection can incite a stronger inflammatory reaction in the periportal region. However, it is impossible to diagnose a primary biliary tract infection from a liver biopsy alone. Aerobic and anaerobic culture and cytological examination of bile are required to diagnosis infectious cholangitis.

Surgical goals are to relieve biliary obstruction or leakage and restore bile flow. Reconstructive procedures to divert bile flow can be performed if the cause of EBDO cannot be corrected. However, because these carry a poor long-term prognosis, less invasive procedures such as stenting are preferred whenever possible (Amsellem et al., 2006).

Antibiotic therapy is started immediately after bile samples are obtained; ampicillin or amoxicillin (22 mg/kg IV, SQ, or PO q8h), first-generation cephalosporins (22 mg/kg IV or PO q8h), or metronidazole (7.5 to 10 mg/kg PO q12h; use lower dose when severe hepatobiliary dysfunction is present) are good empiric choices as single agents initially in animals without a long history of antibiotic administration.

In cases without complete biliary obstruction (e.g., ascending cholangitis) or with transient obstruction (e.g., some cases of acute-on-chronic pancreatitis), medical management alone is indicated. The choleretic ursodiol is indicated as additional treatment in these cases, provided that complete EBDO has been ruled out. The recommended dose is 10 to 15 mg/kg total daily, preferably split into two doses. In addition, all cases (both medical and surgical) should receive antioxidant therapy, preferably with vitamin E (400 IU for a 30-kg dog, scaled appropriately to the size of the dog; tablets usually come as 100 IU, 200 IU, or 400 IU) and S-adenosylmethionine (20 mg/kg PO q24h) because it has been demonstrated that bile reflux in the liver is a potent oxidant toxin. Dogs should be fed a high quality diet which is not protein-restricted: in most cases, a diet designed for critical care feeding is more appropriate than a manufactured liver support diet, because the dog is suffering an inflammatory and/or septic process whereas hepatocyte function is usually good.

The prognosis for dogs with EBDO or bile peritonitis depends on the underlying cause. If the cause can be addressed without surgical reconstruction, the prognosis is fair to good. If extensive biliary reconstruction is needed, the prognosis is guarded.

#### CONGENITAL VASCULAR DISORDERS

Congenital disorders of hepatic vasculature, both intrahepatic and extrahepatic, are more common in dogs than in cats. There are some breed-related tendencies, suggesting a genetic basis to some disorders, but it is also assumed that most of them result from some type of (as yet undefined) insult in utero. It is known that experimental reduction in flow in the umbilical vein in sheep and other species can result in the development of PSSs and asymmetry of hepatic lobular and vascular supplies; this is likely also true in dogs. This would explain why it is relatively common to see dogs with more than one co-existent congenital vascular disorder in the liver (e.g. a congenital PSS combined with intrahepatic portal vein hypoplasia or microvascular dysplasia [MVD]) and would also explain why dogs with congenital PSSs have a higher prevalence of other congenital defects, such as cryptorchidism and cardiac disorders.

For ease of categorization and because they have different clinical presentations, congenital vascular disorders have been divided into disorders associated with low portal pressure and those with high portal pressure. However, it is important to remember than when two or more congenital hepatic defects occur concurrently, the differentiation will be less obvious.

### CONGENITAL VASCULAR DISORDERS ASOCIATED WITH LOW PORTAL PRESSURE: CONGENITAL PORTOSYSTEMIC SHUNT

### **Etiology and Pathogenesis**

Congenital PSSs are the most common congenital portovascular disorder in dogs. The etiology and pathogenesis are very similar to those in cats; the reader is referred to Chapter 37 for more details. Many different types of congenital portovascular anomalies have been reported in dogs; sometimes they co-exist with intrahepatic or extrahepatic portal vein hypoplasia or intrahepatic MVD (discussed in more detail later). However, a distinguishing feature of isolated congenital PSS is that it results in low portal pressure, because some blood is shunted away from the high resistance sinusoidal circulation by the shunting vessel. Dogs with isolated congenital PSS therefore do not present with ascites unless they are severely hypoalbuminemic. This allows differentiation from the congenital vascular disorders associated with increased portal pressure, and therefore acquired PSS, outlined below, in which portal hypertension and associated ascites are common at presentation.

Canine congenital PSS can be extrahepatic or intrahepatic. Extrahepatic PSSs are anomalous vessels connecting the portal vein or one of its contributors (left gastric, splenic, cranial or caudal mesenteric, or gastroduodenal veins) to the caudal vena cava or azygos vein. They are most commonly recognized in small-breed dogs and have a high prevalence in Cairn Terriers, Yorkshire Terriers, West Highland White Terriers, Maltese, Havanese, other terriers, and Miniature Schnauzers (Fig. 38-9). Intrahepatic PSSs may be left-sided, in which case they are thought to represent persistence of the fetal ductus venosus, or they can be right-sided or central, in which case they likely have a different embryological origin. Intrahepatic PSS is more commonly seen in large-breed dogs, but Collies also tend to have extrahepatic PSSs, despite being large dogs. Increased breed prevalence suggests a genetic basis to the disease, but this has only been investigated in Irish Wolfhounds, in which an inherited basis of



**FIG 38-9**Typical small-breed dogs with congenital extrahepatic portosytemic shunts. **A,** An 8-month-old female Border Terrier. **B,** A 9-month-old female Miniature Schnauzer.

patent ductus venosus has been demonstrated, and in Cairn Terriers with extrahepatic PSS, in which an autosomal polygenic inheritance or monogenic with variable expression is suspected (Van Straten et al., 2005). Affected Irish Wolfhounds tend to have smaller litters and can also produce more than one puppy with a PSS in a litter.

One study reported that dogs from breeds that were not usually recognized as having a high risk of PSS were more likely to present with unusual anatomical forms of PSS that were less often amenable to surgical management (Hunt, 2004).

### **Clinical Features**

Clinical signs are very similar to those in cats; neurological, gastrointestinal, and urinary tract signs predominate (see Chapter 37 for more details). About 75% of dogs present before 1 year of age, but some present at an older age, with some as old as 10 years of age before signs are recognized. There is a spectrum of severity of neurological signs ranging from severely affected young puppies that persistently circle, become centrally blind, and can even have seizures or become comatose to very mildly affected individuals. It is likely that this variation reflects differences in shunt fraction and also dietary and other environmental differences among dogs. Polydipsia and polyuria with hyposthenuric urine are relatively common; this is largely due to high cortisol concentration in affected dogs (see Chapter 35) and also increases in antidiuretic hormone and reduced renal medullar concentrating gradient (see Chapter 35). Urate uroliths are also common and can be renal. Anecdotally, urate renal calculi seem to be more common in terriers, and dogs presenting with calculi often do not have prominent neurological signs. On physical examination animals are often (but not always) smaller than their littermates and may have non-localizing

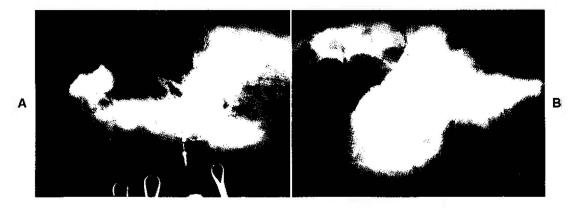
neurological signs and (in some cases) palpable renomegaly. The latter is due to circulatory changes and is not a reflection of renal disease; it is of no clinical significance and regresses after shunt ligation. Other congenital defects may be apparent, particularly cryptorchidism.

#### Diagnosis

Diagnosis of congenital PSS in dogs is the same as in cats (see Chapter 37) and relies on visualizing the shunting vessel ultrasonographically, with portovenography (Fig. 38-10), or grossly at surgery. Scintigraphy can demonstrate shunting but is not helpful to differentiate congenital from acquired PSS, so some other imaging method is necessary for treatment decisions. See Chapter 36 for more information on imaging PSS.

It is important, if possible, to try to estimate how well-developed the remaining hepatic portal vasculature is by repeating the portovenography after ligation and/or by evaluating the histological findings on liver biopsies taken at the time of ligation. This is a work in progress, but there is a strong suspicion that the prognosis postligation may depend on the potential for the intrahepatic vasculature to open up after surgery and that dogs that do poorly postoperatively may have concurrent portal vein hypoplasia and/or MVD (discussed in more detail later).

Nonspecific clinicopathologic findings in more than 50% of affected dogs, regardless of the type of vascular anomaly, are microcytosis, hypoalbuminemia, mild increases in serum AP and ALT activities, hypocholesterolemia, and low BUN concentration. Fasting bile acid concentrations may be normal or high, but postprandial bile acid concentrations are high in all cases. However, this does not distinguish congenital PSS from acquired PPS or early cholestasis, which also causes increases in bile acid concentrations. Postpran-



**A,** Portovenogram in a 1-year-old Golden Retriever with an intrahepatic portosystemic shunt. This was a central divisional shunt and had a venous sinus-like structure, as demonstrated well in this radiograph. **B,** Normal portovenogram in a dog for comparison. (Courtesy the Diagnostic Imaging Department, the Queen's Veterinary School Hospital, University of Cambridge.)

dial ammonia concentration can also be measured and will be high, whereas fasting ammonia concentration may be high or normal (see Box 36-1 for details of how to perform an ammonia challenge test). Ammonia tolerance or challenge tests are potentially dangerous because they can precipitate an encephalopathic crisis. Other tests have been evaluated for their sensitivity and specificity in the diagnosis of PSS. Protein C, a liver-derived anticoagulant factor, is also decreased in dogs with PSS and increases after ligation; this can help differentiate PSS from MVD.

Puppies of high-risk breeds could be screened for congenital PSS by measuring bile acid or ammonia concentrations before they are placed into homes, but there are potential false positives with both of these tests and no puppy should be euthanized or labeled as having a definite congenital PSS on the basis of high bile acid and/or ammonia concentrations without further evidence. Normal Irish Wolfhounds can have a transiently high blood ammonia concentration between the ages of 6 to 8 weeks; this normalizes at 3 to 4 months of age. Zandlivet et al. (2007) have demonstrated that this is due to a clinically insignificant urea cycle defect. Postprandial bile acid concentrations can be falsely elevated in Maltese puppies without PSS for unknown reasons, again confusing any efforts at screening tests in this breed (Tisdall et al., 1995).

On diagnostic imaging the liver is frequently (but not always) small. Ultrasonography now has a high sensitivity and specificity for the diagnosis of both intrahepatic and extrahepatic PSS; furthermore, their anatomy can usually also be described ultrasonographically.

### **Treatment and Prognosis**

Surgical occlusion of the anomalous vessel to restore normal portal circulation has long been recommended as the treatment of choice. In many cases this will restore normal or near normal liver function. However, owners need to be aware of the small but definite risk of postoperative mortality as a result of portal hypertension and/or refractory seizures and of the potential that the PSS may be only partially and not totally ligated. In fact, it is more common to be able to partially ligate the PSS at the first surgery because the portal vasculature cannot initially accommodate all the shunting blood. In some cases it is possible to repeat the surgery at a later date to ligate the PSS further, but this is often not necessary to control clinical signs. A few dogs with partially ligated shunts develop portal hypertension and multiple acquired PSS with a recurrence of their clinical signs. There are several different surgical procedures described for ligation of PSS, but they are outside the scope of this book. In addition to surgical ligation, PSS may be attenuated with ameroid constrictors (Fig. 38-11) or embolized with coils. Laparoscopic ligation of PSS has been reported in two dogs (Miller et al., 2006). Ligation of a PSS requires an experienced surgeon.

Medical management is required to stabilize the patient before surgery and also for about 8 weeks after surgery while the hepatic vasculature and mass recover. This involves careful dietary management combined, in many cases, with antibiotics and soluble dietary fiber. The details are outlined in Chapter 39. In some cases medical management may continue successfully over the course of the patient's life as an alternative to surgery (Watson et al., 1998). Usually, this is because the client cannot afford referral or is unhappy about the risks associated with surgery or because the patient has multiple or intrahepatic shunts. Mildly affected and older animals are good candidates for medical management; generally, these are the individuals with smaller shunting fractions. Dogs (particularly terriers) that present at an older age with urate stones but no neurological signs, are also good candidates for medical management alone. In addition, dogs with concurrent portal vein hypoplasia and/or MVD tend to have a higher surgical risk and are best managed medically.

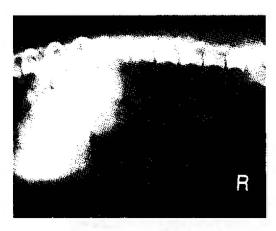


FIG 38-11

Lateral abdominal radiograph of a 3-year-old Miniature Schnauzer that had an extrahepatic portosystemic shunt ligated with an ameroid constrictor 2 years previously. Note the ameroid is visible as a radiodense ring in the craniodorsal abdomen. (Courtesy the Diagnostic Imaging Department, the Queen's Veterinary School Hospital, University of Cambridge.)

Medical management does not reverse the underlying disorder but can result in good long-term results. Once the dog has reached adulthood, there is no evidence that the liver progressively atrophies throughout life. Ultimately, more studies are needed to identify the factors that are most important in determining prognosis after medical and/or surgical management and to help identify preoperatively the small number of animals that will have a poor outcome after surgery.

# CONGENITAL VASCULAR DISORDERS ASSOCIATED WITH HIGH PORTAL PRESSURE

There are a number of less common congenital vascular disorders of the liver in dogs that present with normal or high portal pressure, rather than the low portal pressure seen in association with congenital PSS. Because of the portal hypertension, the affected dog may present with the constellation of typical clinical signs (see Chapter 39), including ascites, and the potential for GI ulceration in addition to multiple acquired PSS and HE. With the exception of arteriovenous fistulae, none of these conditions can be treated surgically; however, some of them have a good long-term prognosis with medical management.

### Primary Hypoplasia of The Portal Vein/ Microvascular Dysplasia/Noncirrhotic Portal Hypertension

### **Etiology and Pathogenesis**

There are several reports of vascular disorders in young dogs associated with portal hypertension, usually ascites, and characteristic histopathological changes in the liver of a reduction in smaller portal vein branches, increased numbers of arterioles, and a variable amount of mild fibrosis. There are some reports of overt hypoplasia of the extrahepatic portal vein, but most reports of noncirrhotic portal hypertension and MVD appear to describe portal vein hypoplasia confined to the intrahepatic vasculature. These diseases may all be different abnormalities or they may represent different spectra of the same abnormalities, but their clinical presentation, treatment, and prognosis are similar. A lack of intrahepatic or extrahepatic portal vein branches results in portal hypertension, with the same potential consequences as those of chronic hepatitis (see preceding section), including ascites, gut wall edema, and often GI ulceration and acquired PSS. Dogs with MVD often do not present with notable portal hypertension, but it is grouped with these diseases by the WSAVA liver standardization group (Cullen et al., 2006). Dogs reported with MVD typically have shunting at the level of the hepatic lobule but do not have clinical signs of overt portal hypertension.

Any breed can be affected, but MVD particularly affects small-breed dogs, with Yorkshire Terriers and Cairn Terriers showing a particularly high incidence.

### **Clinical Signs**

Dogs with all these conditions typically present at a young age with a combination of signs of portal hypertension and PSS, the severity of which depends on that of their lesions. Because of the acquired PSS seen in these patients, some of the clinical signs and clinicopathologic findings overlap with those of congenital PSS, particularly because all these disorders typically present in young dogs. Therefore presence of other signs of portal hypertension (e.g., ascites) is an important clinical clue that one of these disorders with acquired PSS may be present, rather than a congenital PSS.

Dogs with portal vein hypoplasia or idiopathic noncirrhotic portal hypertension typically present between 1 and 4 years of age and are often purebreds of either gender; large breeds predominate. Early reports of "congenital" or juvenile hepatic fibrosis in German Shepherd Dogs may also have represented a form of noncirrhotic portal hypertension. Presenting signs are typically those of portal hypertension, with abdominal distention associated with effusion; GI signs; polydipsia; weight loss; and, less consistently, signs of HE. Dogs are often surprisingly alert (Fig. 38-12).

Dogs with MVD present with similar clinicopathological findings but usually without overt evidence of portal hypertension or ascites. MVD tends to affect terriers and thus overlaps with breeds at high risk for congenital PSS. In addition, some dogs may have both congenital PSS and MVD or portal vein hypoplasia, further confusing the diagnosis. Cairn Terriers and Yorkshire Terriers in particular have been reported with MVD. In one breed (the Cairn Terrier), the site of anatomic abnormality has been identified as the terminal portal veins. In this breed it is believed to be an autosomal, inherited trait, but the specific mode of inheritance has not been established. Typical signs include vomiting, diarrhea, and signs of HE, although the clinical signs, particularly the HE, are notably milder in dogs with MVD than



#### FIG 38-12

A female German Shepherd Dog with noncirrhotic portal hypertension. **A,** At 14 months of age, with ascites and in poor body condition but remarkably alert **B,** 5 years later on medical management only—very stable and in good body condition with no detectable ascites. The dog lived for 8 years with a good quality of life before developing a gastroduodenal ulcer (see Chapter 39). **C,** Drugs that the dog received long term, in addition to dietary management. (B and C reproduced by permission from *UK Vet*, 9(7):41, 2004.)

in those with congenital PSS unless both disorders occur concurrently. Dogs with only MVD are somewhat older, and many have mild to no signs of illness. In the case of young purebred dogs that have been screened for congenital PSS before sale or that are ill for nonhepatic reasons, high SBA concentration may be the only finding.

#### **Diagnosis**

Diagnosis of MVD/intrahepatic portal vein hypoplasia and noncirrhotic portal hypertension relies ultimately on liver biopsy findings of intrahepatic portal vein hypoplasia in the absence of a grossly demonstrable shunting vessel. The liver biopsy findings alone can be indistinguishable from the changes that occur secondary to congenital PSS, and therefore the clinical findings of concurrent portal hypertension and ruling out a shunting vessel are important parts of the final diagnosis. Clinicopathologic findings are very similar to those in dogs with congenital PSS and include microcytosis, evidence of hepatic dysfunction (e.g., hypoalbuminemia), and low urine specific gravity. Microhepatia and hypoechogenic abdominal fluid are the notable abdominal ultrasonographic findings in dogs with noncir-

rhotic portal hypertension; it may be possible to visualize multiple acquired PSSs ultrasonographically. Dogs with MVD alone tend not to have ascites and have less marked increases in SBA concentrations than dogs with true congenital PSS.

The most important aspects of identifying a dog with MVD/portal vein hypoplasia/noncirrhotic portal hypertension are ruling out a surgically correctable PSS, identifying portal hypertension (which requires treatment, see Chapter 39), and obtaining a liver biopsy for confirmation or exclusion of other hepatopathies. Portal vein hypoplasia and noncirrhotic portal hypertension are very similarly clinically, on clinical pathology, and on diagnostic imaging to end-stage chronic hepatitis with cirrhosis, and the only way to differentiate the two is on liver histology. In general, portal vein hypoplasia/noncirrhotic portal hypertension carries a much better long-term prognosis than cirrhosis, so the differentiation is important prognostically.

#### **Treatment and Prognosis**

The prognosis for all these conditions appears to be relatively good, provided the clinical signs can be controlled. They are

nonprogressive, and there is no surgical treatment for any of them; symptomatic therapy of HE, ascites, and GI ulceration (if present) is usually successful (see Chapter 39). It should be noted that glucocorticoid therapy is absolutely contraindicated in these dogs and is likely to worsen the outcome because of the associated portal hypertension and high risk of GI ulceration. This underlines the importance of liver biopsy in these dogs, allowing differentiation from chronic hepatitis.

One study of dogs with noncirrhotic portal hypertension concluded that affected dogs might live as long as 9 years after diagnosis with appropriate symptomatic therapy. A few dogs were euthanized because of problems related to persistent portal hypertension (e.g., duodenal ulceration). Dogs with MVD tend to have milder clinical signs than dogs with congenital PSS and can be managed medically with success over the long term. Affected dogs seem to live comfortably in good to excellent condition for at least 5 years (Christiansen et al., 2000).

### Arterioportal Fistula

Intrahepatic arterioportal fistula, causing marked volume overload of the portal circulation resulting in portal hypertension, acquired PSSs, and ascites, is seen occasionally. Abdominal ultrasonography with Doppler can frequently detect the tortuous tubular structures representing the connection between an artery and overperfused portal vein or veins; sometimes the turbulent blood flow through the fistula can be auscultated through the body wall. If only one lobe of the liver is affected, the lobe containing the arterioportal fistula can be removed surgically; assuming that there is adequate intrahepatic portal vasculature, acquired PSSs regress once portal overcirculation subsides. More often, multiple liver lobes are involved, making surgical treatment impossible.

### **FOCAL HEPATIC LESIONS**

### **ABSCESSES**

### Etiology

Hepatic abscesses are usually the result of septic embolization from an intraabdominal bacterial infection. In puppies they are a frequently a consequence of omphalophlebitis, whereas in adult dogs they arise most often subsequent to inflammatory conditions of the pancreas or hepatobiliary system. Adult dogs with certain endocrine diseases, such as diabetes mellitus or hyperadrenocorticism, are also at risk. Occasionally, infection arising from a location other than the abdominal cavity, such as the endocardium, lung, or blood, may disseminate to the liver, causing abscessation.

In a review (Farrar et al., 1996) of 14 dogs with hepatic abscesses, aerobic bacteria were isolated in 9 of 10 cases in which material from the hepatic lesions was submitted for culture. Although the most common isolates were gramnegative organisms, *Staphylococcus* spp. were identified in

two dogs. *Clostridium* sp. was the only isolate cultured anaerobically from abscess fluid in 4 of 7 dogs.

#### **Clinical Features**

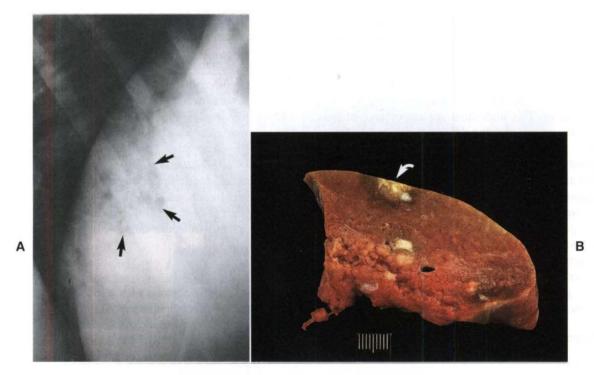
The typical signalment and physical examination findings in dogs with hepatic abscesses depend on the underlying cause. Dogs over 8 years old are most often affected because the predisposing causes of liver abscesses are seen more commonly in older dogs. Regardless of the initiating event, anorexia, lethargy, and vomiting are consistent presenting complaints. Expected physical examination findings include fever, dehydration, and abdominal pain. Hepatomegaly may be detected in dogs with diabetes mellitus or hyperadreno-corticism and in some dogs with primary hepatobiliary disease.

### Diagnosis

Neutrophilic leukocytosis with a left shift, with or without toxic changes, and high serum ALP and ALT activities are dependable but nonspecific clinicopathologic abnormalities. Survey abdominal radiographs may reveal evidence of irregular hepatomegaly, a mass, or gas opacities within the area of the hepatic parenchyma (Fig. 38-13), but ultrasonography is the imaging modality of choice. One or more hypoechoic or anechoic hepatic masses and perhaps a hyperechoic rim surrounding the mass or masses are characteristic findings. If there are multiple masses that would preclude surgical removal or if the owner declines surgery, FNA cytologic analysis of the contents of a representative lesion will distinguish an abscess from nodular hyperplasia, neoplasm (e.g., hemangiosarcoma), or granuloma. Ideally, material should be obtained for cytologic analysis and aerobic and anaerobic bacterial culture from a representative lesion deep in the liver parenchyma to prevent abscess rupture and abdominal contamination. Abscess material should also be obtained by this approach during surgery so that antibiotic treatment can be initiated postoperatively. Ultrasound-guided drainage of the abscess can also be used as treatment in combination with appropriate antibiotics (discussed in more detail later). Results of the preliminary clinicopathologic and radiographic evaluation should be scrutinized for evidence of previously mentioned associated or predisposing illnesses.

### **Treatment and Prognosis**

Treatment for liver abscesses consists of surgical removal of infected tissue, administration of appropriate antibiotics, supportive care, and resolution of underlying predisposing conditions. Infected liver tissue should be removed, if possible, and submitted for histopathologic examination and bacterial culture if this was not done preoperatively. Fluid, electrolyte, and acid-base abnormalities are addressed. Administration of a combination of antibiotics with a gramnegative and anaerobic spectrum is initiated until culture and sensitivity test results are available. Because staphylococci and clostridia are the most common isolates, amoxicillin (10 to 20 mg/kg IV q8h) or enrofloxacin (2.5 mg/kg IV or PO q12h) combined with metronidazole (10 mg/kg PO



**FIG 38-13 A,** Lateral abdominal radiograph of a 1-year-old female Great Dane with a liver abscess (arrows) caused by Clostridium spp.; the cause was undetermined. **B,** Gross appearance of the resected liver lobe containing an abscess (arrow).

q8-12h or 7.5 mg/kg PO q8-12h for dogs with hepatic dysfunction) or clindamycin (10 mg/kg IV or PO q12h) is a good empiric choice. Surgery is not indicated in animals with multiple abscesses; ultrasound-guided centesis and abscess evacuation may be a reasonable adjunct to treatment. Antibiotic treatment is continued on a long-term basis, usually for 6 to 8 weeks or until clinicopathologic and ultrasonographic indicators of abscessation are resolved. From the limited information available about this rare condition, it seems that with aggressive medical and surgical management the prognosis for dogs with liver abscesses may not be as poor as once thought.

#### **NODULAR HYPERPLASIA**

Hepatic nodular hyperplasia is a benign condition of older dogs that does not cause clinical illness; clinicians should be aware of it, however, because hyperplastic nodules may be misinterpreted as a more serious condition, such as primary or metastatic malignancy or regenerative nodules associated with cirrhosis. The prevalence increases with age, and as many as 70% to 100% of dogs older than 14 years of age have some microscopic or macroscopic hyperplasia. Affected dogs have high serum ALP activity (usually 2.5-fold elevation but may be as high as fourteenfold), which prompts investigation for hyperadrenocorticism. There is no evidence of hepatic dysfunction on serum biochemical analysis. Many dogs have multiple macroscopic nodules found ultrasonographically or at surgery, ranging in size from 2 to 5 cm in diameter; some dogs have a single nodule. Micronodular

change occurs much less frequently and would be identified in liver biopsy specimens. The lesion consists of increased numbers of normal to vacuolated hepatocytes with more mitotic figures and fewer binucleate cells than expected in normal liver; components of normal lobular architecture (e.g., portal tracts, central vein) remain. Adjacent parenchyma is compressed by growth of the nodules; fibrosis, necrosis, inflammation, and bile ductule hyperplasia are absent. Because the prognosis for each of these nodular conditions is different and the margin of the lesion with adjacent hepatic tissue is important to establish a diagnosis, a wedge biopsy is recommended. Needle specimens are likely to be too small to confidently differentiate nodular hyperplasia from primary hepatocellular carcinoma or adenoma. The cause of this lesion is unknown; on the basis of experimental development of nodular hyperplasia in rodent species, some have speculated a dietary role (low protein).

#### **NEOPLASIA**

### Etiology

Primary hepatic neoplasms are rare in dogs, accounting for fewer than 1.5% of all canine tumors. Unlike in cats, malignant tumors are more common than benign tumors, and metastatic tumors are 2.5 times more common than primary tumors in dogs. Metastases particularly arise from primary neoplasms in the spleen, pancreas, and GI tract (Fig. 38-14); the liver can also be involved in systemic malignancies such as lymphoma, malignant histiocytosis, and mastocytosis.

Although certain chemicals can induce hepatic neoplasms experimentally and infectious hepatitis is also a predisposing cause in other species, the cause of naturally occurring canine hepatic neoplasms is unknown. The types of primary hepatic tumors seen in dogs and their relative importance and metastatic potential are outlined in Table 38-3.

### **Clinical Features**

Clinical signs and physical examination findings in dogs with primary or secondary liver tumors are nonspecific, except for diffuse or nodular hepatomegaly. Even this can be confused with other conditions, such as macronodular cirrhosis or benign nodular hyperplasia, which are also common in older dogs. Therefore no dog should be euthanized on the basis of a presumptive diagnosis of a liver mass on clinical



FIG 38-14
Gross appearance of liver post-mortem from a 2-year-old male Husky with a metastic carcinoma.

examination or diagnostic imaging without supportive histology. The left liver lobes are often affected by hepatocellular carcinoma which can occur in three different patterns: massive (single, large nodule; most common), nodular (multiple smaller nodules), and diffuse (indistinct nodules throughout). The behavior of each type of tumor tends also to be different, as outlined in Table 38-3.

Clinicopathologic abnormalities are likewise not specific for neoplasia and blood tests may be normal, even in dogs with extensive involvement. Dogs with lymphoma infiltrating the liver usually have marked increases in ALT and ALP activities but are rarely jaundiced; moreover, they may have normal liver echotexture. Hypoglycemia has been described in association with hepatocellular carcinoma in dogs and can be due to paraneoplastic production of insulin-like growth factor. Massive forms of hepatocellular carcinoma have a low metastatic rate. Metastases from other diffuse and nodular forms of hepatocellular carcinoma or biliary carcinoma usually occur early; the most common sites are regional lymph nodes, lung, and peritoneal surfaces. Hepatocellular adenoma (hepatoma) is a benign tumor that most often occurs as a single mass that is typically smaller than the massive form of hepatocellular carcinoma but can be multifocal. Histologic features of hepatocellular adenoma are very similar to those of nodular hyperplasia (or indeed normal liver) except for the presence of a fine rim of reticulin surrounding the adenoma and lack of apparent normal architecture (i.e., few portal tracts, no central veins).

### Treatment and Prognosis

When a single large hepatic mass is identified, it can be very difficult to distinguish well-differentiated hepatocellular carcinoma from nodular hyperplasia and hepatocellular



**TABLE 38-3** 

### Primary Liver Tumors in Dogs

Note that malignant tumors are more common than benign tumors and that metastases to the liver are more common than primary liver tumors in dogs.

### TYPE OF TUMOR

Hepatocellular tumors: Hepatocellular carcinoma (HCC) Hepatocellular adenoma/hepatoma (Hepatoblastoma—very rare)

Biliary tract tumors:

Biliary carcinoma (including cystadenocarcinoma) Biliary adenoma Gallbladder tumors

Neuroendocrine tumors:

Hepatic carcinoid

Primary hepatic sarcomas:

Hemangiosarcoma, leiomyosarcoma, and others

### COMMENTS

HCC most common primary liver tumor in dogs (50%). Most are massive; some are nodular or diffuse. Miniature Schnauzers and male dogs may be at increased risk. MR 0% to 37% for massive and 93% to 100% for nodular and diffuse forms.

Adenoma uncommon and usually incidental.

Bile duct carcinomas second most common primary tumor in dogs (22% to 41% of malignant canine liver tumors). Labrador Retrievers and females may be at increased risk. Usually aggressive. MR up to 88%. Adenomas uncommon and gallbladder tumors very rare. Very rare, but always diffuse or nodular, and very aggressive.

Uncommon. Most locally aggressive, diffuse or nodular and high MR.

adenoma. Surgical resection is the treatment of choice for primary hepatic neoplasms and for massive hepatocellular carcinoma. In the latter, it usually carries a good prognosis because they have a lower metastatic rate than the more diffuse and nodular forms of the tumor and local recurrence rate after liver lobectomy is reportedly less than 13%. Longterm (2- to 3-year) survival rates after surgical resection are common in dogs with massive hepatocellular carcinoma Surgical excision is therefore the treatment of choice for single tumors involving one liver lobe because this allows both diagnosis and, in many cases, cure. The prognosis for diffuse and nodular hepatocellular carcinoma and other forms of primary malignant liver tumors is poor because there is no effective therapy. Radiation therapy is not effective because the liver cannot tolerate cumulative doses of radiation. Hepatic tumors also respond poorly to chemotherapy, likely partly because of development of rapid drug resistance by neoplastic hepatocytes. The response of secondary (metastatic) liver tumors depends on the type and location of the primary; responses in dogs with lymphoma are very good to excellent, and in dogs with hemangisoarcoma they are good. Metastatic carcinomas or carcinoids of the liver rarely respond to chemotherapy.

### HEPATOCUTANEOUS SYNDROME/ SUPERFICIAL NECROLYTIC DERMATITIS

### **Etiology and Pathogenesis**

Hepatocutaneous syndrome (also known as superficial necrolytic dermatitis, metabolic epidermal necrosis, and necrolytic migratory erythema) is a skin condition reported in association with certain liver diseases that usually carries a poor prognosis. The pathophysiology and underlying causes in dogs remain unclear, and it is likely multifactorial. It occurs in association with certain classical findings on hepatic ultrasonography and histopathology, and often no underlying cause is found. However, because it is likely that many cases represent a hepatic reaction to an underlying endocrine tumor or disorder, superficial necrolytic dermatitis represents an intermediate disorder between primary liver disease and secondary hepatopathies.

The underlying pathogenesis in the skin appears to be due to abnormally low circulating amino acid concentrations and thus malnutrition of the skin, particularly in areas of poor blood supply, such as the extremities. Zinc deficiency may also be involved because the histological appearance of the skin is very similar to that in dogs with zinc-responsive dermatosis; fatty acid deficiencies have also been implicated. In humans the disorder is usually associated with a glucagon-secreting tumor of the pancreas. However, glucagonomas are rarely reported in affected dogs, and circulating glucagon concentrations are usually normal (although they may be occasionally high). Plasma amino acid concentrations have been reported to be very low in all affected dogs in which they have been measured, both in dogs with pan-

creatic tumors and dogs without. It has been proposed that canine superficial necrolytic dermatitis represents a metabolic hepatopathy with increased hepatic catabolism of amino acids that decreases their peripheral availability.

Recently, 11 dogs with superficial necrolytic dermatitis secondary to chronic phenobarbital administration for epilepsy were reported (March et al., 2004). The median age of the affected dogs was 10 years, and the median duration of phenobarbital therapy was 6 years. No other underlying cause could be found. Plasma amino acid concentrations were markedly decreased in the only dog in which they were measured.

Whatever the underlying pathogenesis, dogs with superficial necrolytic dermatitis are at high risk of becoming diabetic, which is reported in 25% to 40% of cases. This is easy to explain if blood glucagon concentrations are high, because glucagon is a diabetogenic hormone, but is difficult to explain on the basis of simple amino acid alterations.

### **Clinical Findings**

Idiopathic superficial necrolytic dermatitis is reported most often in older dogs of small breeds; in one study 75% of the affected dogs were male (Outerbridge et al., 2002). Most dogs present because of their skin disease rather than their primary liver disease. Typically, there is erythema; crusting; and hyperkeratosis affecting the footpads, the nose, and periorbital, perianal, and genital areas and also often pressure points on the limbs. The paw lesions can be extremely painful because of associated fissures and may result in lameness and secondary infection. Signs of liver disease may also be present (although usually not), and diabetes mellitus often develops later in the disease process, especially if the animal is given diabetogenic drugs such as glucocorticoids in an attempt to control the skin disease.

### **Diagnosis**

Definitive diagnosis is based on skin biopsy findings that are very characteristic and unique: The only syndrome with a similar appearance on skin histopathology is zinc-responsive dermatosis. There is a marked parakeratotic hyperkeratosis with intercellular and intracellular edema and hyperplastic basal cells, producing a characteristic "red, white, and blue" appearance on hematoxylin and eosin staining.

The associated hepatic findings are more nonspecific, except for the ultrasonographic findings. There are usually increases in liver enzyme activities, and there may be hypoalbuminemia in some cases. In dogs that are diabetic there is hyperglycemia and glycosuria. The classical ultrasonographic appearance is a "Swiss-cheese" liver consisting of multiple hypoechoic regions with hyperechoic borders (Fig. 38-15). Hepatic histology in all cases is remarkably similar, showing what has been described as a distinctive form of macronodular cirrhosis. The liver is divided into regenerative hyperplastic nodules with fibrous septa and bordered by characteristic ballooned, vacuolated hepatocytes but with minimal or no inflammation or necrosis.



### FIG 38-15

Ultrasonographic appearance of the liver of a 6-year-old Border Terrier with hepatocutaneous syndrome secondary to chronic phenobarbital medication for idiopathic epilepsy. Note the typical hypoechoic "holes" in the liver parenchyma on the left. (Courtesy Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge.)

### **Treatment and Prognosis**

The prognosis is very poor unless the underlying cause can be identified and treated; most dogs live for less than 6 months. There have been reports of resolution of disease if a pancreatic tumor is identified and removed. Dogs with phenobarbital-associated hepatocutaneous syndrome may improve when the drug is withdrawn, although this has not yet been demonstrated. An alternative nonhepatotoxic therapy for their epilepsy will need to be instituted; potassium bromide might be an alternative choice, but it takes weeks to reach steady-state. Gabapentin might also be used, although this is only effective in some dogs. For additional information, please see Chapter 67.

When an underlying cause cannot be identified and treated, therapy is symptomatic and supportive. The most important aspect is amino acid/protein supplementation; in a few cases this may lead to long-term survival. There are single case reports of humans with resolution of the disease after amino acid infusions and/or regular dietary supplementation of egg protein; feeding egg yolks has also been reported as resulting in a clinical improvement in some dogs. It is unclear whether eggs are beneficial simply because they are a high-quality amino acid supplement or whether there are other beneficial micronutrients in the eggs. Dogs with hepatocutaneous syndrome should not be fed proprietary diets for liver disease because these are protein restricted. Other support included antibiotics for secondary skin infections (such as cefalexin 20 mg/kg q12h) and antioxidants (see the section on the treatment of chronic hepatitis). In addition, zinc and fatty acid supplementation may be helpful in some cases. Glucocorticoids should be avoided because they will precipitate diabetes mellitus. We have treated two dogs with hepatocutaneous syndrome that survived for several years on a high-quality digestible diet (marketed for GI disease) supplemented with extra egg and vitamin E and S-adenosylmethionine supplementation with antibiotics; however, one dog did become diabetic a month after diagnosis.

### **SECONDARY HEPATOPATHIES**

Secondary (reactive and vacuolar) hepatopathies are very common in dogs. In fact, in pathology studies it is clear that they are more common than primary hepatic disease. Many of these hepatopathies result in elevations in liver enzymes, but the liver changes are usually not clinically significant and usually do not result in compromised liver function. However, they are often confused with primary liver disease, and it is important to rule out secondary hepatopathies as much as possible in the workup of dogs with elevated liver enzymes to allow identification and treatment of the underlying primary disease (e.g., endocrine disease or inflammatory disease elsewhere in the splanchic bed). It is also important to be aware that raised liver enzymes in an old dog have many other causes apart from primary liver disease and to resist the tendency to immediately put such dogs on a protein-restricted diet and other medication for liver disease before working up the case properly. Many dogs with secondary hepatopathies will not have hepatic histopathology performed because the primary cause will be identified with other tests. However, it is convenient from a classification point of view to split secondary hepatopathies into three groups on the basis of their appearance histopathologically: secondary hepatopathies associated with hepatocyte swelling and/or vacuolation, hepatic congestion/edema, and reactive hepatitis.

### **HEPATOCYTE VACUOLATION**

Secondary hepatopathies associated with hepatocyte vacuolation are divided into steroid-induced hepatopathy and hepatocellular steatosis (lipidosis/fatty change). Steroid-induced hepatopathy is characterized by hepatocellular glycogen accumulation, which is distinctive from steatosis, in which fat (rather than glycogen) accumulates in hepatocytes. The difference can be demonstrated with special stains (Periodic acid Schiff for glycogen and Oil red O or Sudan black for fat), but there are some differences also on routine hematoxylin and eosin staining that help with differentiation: Glycogen vacuoles tend not to displace the nucleus from the center of the cell and often contain strands of eosinophilic material, whereas classic steatosis is associated with clear, empty vacuoles (because the fat is lost in processing) and the nucleus is often displaced to the edge of the cell (Fig. 38-16).

Both types of vacuolar hepatopathy are reversible when the underlying cause is taken away. The most common causes are endocrine diseases (see Table 38-1). Steroid-induced hepatopathy is seen in hyperadrenocorticism and dogs being given exogenous corticosteroids. It has also been associated with other hormone therapies and administration of some other drugs, such as D-penicillamine. There have been

FIG 38-16

Gross (A) and histological (B) appearance of the liver postmortem in a middle-aged Miniature Poodle with poorly controlled diabetes mellitus. Note the pale, yellowish appearance of the liver associated with generalized hepatic steatosis. Histologically, the hepatocytes are markedly swollen with fat that displaces the nuclei to the edge of the cells. Portal triad in the center (Hematoxylin and eosin x 200). (Courtesy Pathology Department, Department of Veterinary Medicine, University of Cambridge.)

reports of idiopathic vacuolar hepatopathy in Scottish terriers causing marked elevations in ALP, but the underlying cause is unknown. The vacuolation seen as part of the hepatocutaneous syndrome looks very similar to glycogen vacuolation. Steatosis is classically associated with diabetes mellitus in dogs, in which it starts centrilobularly and then spreads. It has also been reported in juvenile hypoglycemia of small-breed dogs. However, although hepatic steatosis can sometimes appear very marked in dogs, it does not appear to become a clinically significant disease in its own right, unlike in cats, in which primary or secondary hepatic lipidosis are important clinical syndromes (Chapter 37).

#### **HEPATIC CONGESTION/EDEMA**

Hepatic congestion is a common finding with right-sided congestive heart failure and other causes of posthepatic venous congestion, such as heartworm disease. This results again in elevation in liver enzymes. It is usually reversible, but in a few very chronic cases of congestion associated with heart disease, it can result in fibrosis and permanent compromise ("hepatic cirrhosis").

### **NONSPECIFIC REACTIVE HEPATITIS**

Nonspecific reactive hepatitis is a nonspecific hepatic response to a number of extrahepatic processes, particularly inflammatory processes in the splanchic bed such as pancreatitis and inflammatory bowel disease. There is a mild inflammatory infiltrate in the sinusoids and portal areas and/or parenchyma but no associated hepatocyte necrosis or fibrosis and therefore no evidence of primary (significant) hepatitis. This could be viewed as the hepatic equivalent of a "reactive lymph node" and should stimulate a search for an underlying cause.

#### **Diagnosis**

The diagnosis of all types of secondary hepatopathy relies on diagnosing the underlying cause. The clinical signs will be those of the primary cause and not related to the liver. However, sometimes there will be an overlap in clinical signs—notably with hyperadrenocorticism or diabetes mellitus in which the polydipsia, poluria, and abdominal enlargement together with raised liver enzymes might increase the suspicion of primary liver disease. Recognizing that there is a secondary hepatopathy involves initial pattern recognition of the enzyme elevation and clinical signs (e.g., in a dog with polydipsia/polyuria, a pot-belly, and dermatological signs, a pattern of a very marked elevation in ALP and less marked elevation in ALT should raise the suspicion of hyperadrenocorticism). This is followed by appropriate diagnostic tests for the underlying condition. Liver biopsies are usually not indicated or taken. However, there will inevitably be cases with mild or nonclassical changes of the primary condition in which liver biopsies will be taken on suspicion of primary hepatopathy. Finding nonspecific secondary changes in the liver should then stimulate a repeat search for an underlying cause.

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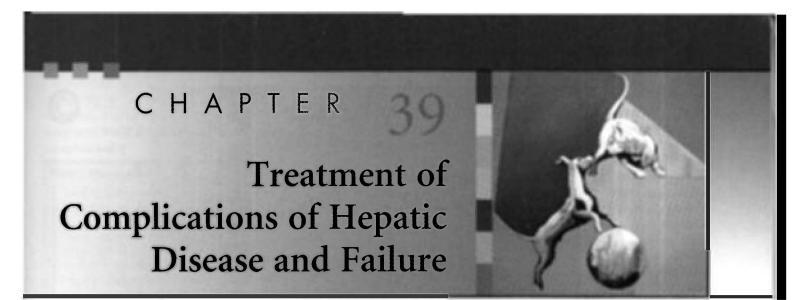
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### CHAPTER OUTLINE

GENERAL CONSIDERATIONS HEPATIC ENCEPHALOPATHY

Chronic Hepatic Encephalopathy Acute Hepatic Encephalopathy PORTAL HYPERTENSION

Splanchnic Congestion and Gastrointestinal Ulceration

Ascites

COAGULOPATHY

PROTEIN-CALORIE MALNUTRITION

### **GENERAL CONSIDERATIONS**

The following problems are common in dogs with hepatic failure and are usually related to sudden or chronic progressive loss of functional hepatocyte mass, intrahepatic portal hypertension resulting from primary hepatobiliary disease, acquired portosystemic shunts (PSSs), or a combination of these factors. The clinical syndrome of portal hypertension with abdominal effusion, acquired PSSs, and high risk of gastrointestinal (GI) ulceration is observed frequently in dogs with chronic liver disease but rarely in cats, whereas coagulopathies are common in cats because of the additional effects of concurrent biliary tract, pancreatic, and small intestinal disease. Hepatic encephalopathy (HE) resulting from congenital PSS is relatively common in both species. Protein-calorie malnutrition is common in both species, particularly in association with chronic disease. Effective management of these problems is vital to achieve a reasonable quality of life for the patient and to enable hepatic recovery while specific therapy is taking effect or when the underlying cause cannot be eradicated.

### HEPATIC ENCEPHALOPATHY

### CHRONIC HEPATIC ENCEPHALOPATHY

#### **Treatment**

The goal of treatment in cats and dogs with HE is to restore normal neurologic function by decreasing formation of gutderived and peripherally derived encephalotoxins, eliminating precipitating factors, and correcting acid-base and electrolyte abnormalities. A variety of encephalotoxins are implicated in causing HE (see Chapter 35), but the most important from the point of view of treatment is ammonia. It was once believed that the most important source of ammonia was undigested protein in the gut, but emphasis has now shifted to interorgan metabolism of ammonia in patients with HE, whereas dietary protein itself is a less important source (Wright et al., 2007; see Chapter 35). Inflammatory mediators are also thought to be important precipitators of HE in their own right. It is known that clinically relevant episodes of HE in dogs and cats with congenital or acquired PSS are often precipitated not just by feeding but also by stress and infections, emphasizing the role of hypermetabolism, inflammation, and breakdown of body protein in the development of HE. In fact, particularly in dogs with acquired PSS and protein-calorie malnutrition, HE is often triggered by negative nitrogen balance and breaking down muscle mass (Fig. 39-1), and in these circumstances starvation and protein restriction will worsen the HE.

A combination of careful dietary manipulation, locally acting agents that discourage formation of readily absorbable ammonia and hasten evacuation of the intestinal tract, antibiotics to suppress bacterial populations that generate ammonia and other gut-derived encephalotoxins, and treatment of any precipitating cause is the standard approach for long-term management of chronic HE (Box 39-1). Dietary management and treatment of the underlying cause are the most important approaches, but advice has changed over the last few years with respect to protein restriction, and it is now clear that dogs and cats with congenital or acquired PSS have higher protein requirements; long-term feeding of



#### FIG 39-1

**A**, A 9-year-old neutered female German Shepherd Dog with previously stable noncirrhotic portal hypertension treated medically for 8 years presented very depressed with a week-long history of anorexia (same dog as Fig. 38-12 in Chapter 38). **B** and **C**, In spite of immediate institution of tube feeding on admission, the dog rapidly developed fatal septic peritonitis as a result of rupture of an ulcer at the gastroduodenal junction. It was found that the dog had developed asymptomatic pyelonephritis. The referring veterinarian had recognized the hepatic encephalopathy but tried to manage it by starvation for a week which likely increased rather than decreased ammonia production through breakdown of muscle and also increased the risk of GI ulceration because of a lack of intraluminal gut nutrition.

a protein-restricted diet not only is not indicated but will result in protein-calorie malnutrition.

Whether it is due to congenital PSS in dogs and cats or acquired PSS (mainly in dogs), treatment of HE is much the same. The main difference is that acquired PSSs are usually the result of portal hypertension, so treatment of the other manifestations of this and the underlying liver disease will also be necessary in these cases (see the discussion of portal hypertension below). Recent studies in human medicine have questioned the actual efficacy of some of the treatment recommendations for HE, including lactulose. Controlled trials have not been conducted in animals to determine the optimal treatment for HE and for each stage (mild, moderate, severe) of HE; therefore current recommendations are based on studies in human medicine and on anecdotal reports in dogs and cats.

### Diet

The ideal diet for long-term management of HE is the same as the diet recommended in chronic liver disease in dogs; dietary recommendations are outlined in Table 38-2 and Box 39-1. Protein restriction has long been recommended in patients with HE owing to the fact that undigested protein

in the gut broken down by bacteria is a source of gut-derived ammonia. However, as has recently been pointed out, gut bacteria will metabolize only undigested protein that reaches the colon. This should not occur if the protein in the diet is very digestible and not in such excessive amounts that it overwhelms the digestive capacity of the small intestine. There are high amounts of ammonia in the portal circulation, particularly after a meal, but the main source of these is obligate catabolism of glutamine by small intestinal enterocytes as their main energy source, and intestinal glutaminase activity seems to increase for unknown reasons in humans with cirrhosis, increasing gut ammonia production. Studies in dogs with experimental PSS and animals and humans with acquired PSS have actually shown a higher protein requirement than in normal animals or people. Therefore the current recommendation is to feed animals with congenital or acquired PSS normal to only slightly reduced quantities of protein that is highly digestible and of high biological value in order to minimize the amounts of undigested protein reaching the colon and "wastage" of excess nonessential amino acids by transamination or deamination for energy. Some experts recommend that diets should have low amounts of aromatic amino acids, because these have



Long-term Medical Management of Hepatic Encephalopathy

#### **Dietary Management**

- Feed normal amounts (if possible) of high-quality, highly digestible protein to minimize the chance that any protein will reach the colon to be converted into NH3. Some veterinarians recommend increasing branched chain amino acids and reducing aromatic amino acids such as tryptophan, but there is no evidence that changing the dietary levels affects cerebrospinal fluid levels. Consider adding ornithine aspartate, which provides substrates for conversion of NH3 to urea (ornithine) and glutamine (aspartate). Restrict protein only if absolutely necessary to control neurologic signs
- Prevent protein-calorie malnutrition by avoiding prolonged fasting and/or excessive protein restriction because this will lead to hyperammonemia from breakdown of body protein
- Feed little and often to reduce the amount of liver work required and reduce the potential for undigested food to reach the colon.
- Fat: No special recommendations, although it should be fed in normal amounts and not restricted unless clinical steatorrhoea develops (rare). Avoid diets that are very high in fats, particularly with cholestasis or portal hypertension in which gastrointestinal signs may be exacerbated.
- Carbohydrates should be highly digestible as a primary calorie source, reducing the need for hepatic gluconeogenesis from fat and protein.
- Fermentable fiber reduces hepatic encephalopathy in the same way as lactulose. Nonfermentable fiber is also important because it prevents constipation and therefore reduces contact time for colonic bacteria to act on feces and produce ammonia.
- Zinc supplementation may reduce encephalopathy because zinc is used in many metalloenzymes in the urea cycle and in muscle metabolism of ammonia

#### Lactulose

Lactulose is a soluble fiber that acidifies colonic contents, reducing ammonia absorption, and also increases colonic bacterial cell growth, therefore incorporating ammonia in to bacterial cell walls. Cats should be given 2.5 to 5 ml PO q8h; dogs 2.5 to 15 ml PO q8h. Start at the low dose, and titrate to effect (2 to 3 soft stools a day).

#### **Antibiotics**

 Amoxicillin (22 mg/kg PO q12 h) or metronidazole (7.5 mg/kg PO q12h) to reduce gastrointestinal flora and also protect against bacteremia

Identify and Treat Concurrent Infections/Inflammation

been implicated in HE, but in fact there is no evidence that the ratio of dietary aromatic amino acid: branched chain amino acid has any effect on HE. Food should be fed in small amounts and often to avoid overwhelming the ability of the liver to metabolize it. Diets manufactured for dogs with liver disease are a good starting point (Hill's canine LD; Royal-Canin canine hepatic) but are rather protein-restricted, so they should be supplemented with a high-quality protein such as cottage cheese or chicken. An alternative is to feed a veterinary diet marketed for intestinal disease; these diets contain high-quality, highly digestible protein sources (Hill's canine or feline ID; Iam's canine or feline intestinal formula; Royal-Canin canine or feline digestive lowfat). Most, if not all, dogs with congenital or acquired PSS can tolerate normal protein concentrations if other measures are also implemented, as outlined in the subsequent paragraphs and in Box 39-1. A few require more marked restriction in the short term, but every effort should be made to increase to a normal protein concentration over the long term.

#### Lactulose

Lactulose (β-galactosidofructose) is a semisynthetic disaccharide that is not digestible by mammals and therefore passes into the colon, where it is degraded by bacteria into short chain fatty acids (SCFA), particularly lactic and acetic acid. These SCFAs help control signs of HE by acidification of the intestinal contents, which traps ammonium ions in the colon, and by promoting osmotic diarrhea. In addition, SCFAs are used as an energy source by colonic bacteria, allowing them to grow and thus incorporate colonic ammonia into their own bacterial protein, which is subsequently lost with the bacteria in the feces (a type of bacterial "ammonia trap").

The dose is adjusted until there are two to three soft stools per day (see Box 39-1); overdosing results in watery diarrhea. There are no known complications of chronic lactulose use in animals (other than diarrhea). However, the efficacy of lactulose has never been critically evaluated in dogs and cats with HE, and recent studies in humans suggest that it may not be as helpful as previously thought. Lactulose can also be given by enema in animals with acute HE (Box 39-2). Many cats and dogs object strongly to the sweet taste of lactulose; an attractive alternative is lactitol ( $\beta$ -galactosidosorbitol), which is a relative of lactulose and can be used as a powder (500 mg/kg/day in three to four doses, adjusted to produce two to three soft stools daily). Currently, lactitol is available in the United States as a food sweetener, but it has not been studied in dogs and cats with HE.

### **Antibiotic Treatment**

If dietary therapy alone or in combination with lactulose is insufficient to control signs of HE, other medications may be added. Antibacterial drugs that are effective for anaerobic organisms (metronidazole, 7.5 mg/kg administered PO q8-12h; amoxicillin, 22 mg/kg administered PO q12h) are preferable. Antibiotics effective for gram-negative, urca-splitting organisms (neomycin sulfate, 20 mg/kg administered PO q12h) may also be used, although neomycin is more useful



BOX 39-2

### Treatment of Acute Encephalopathic Crisis

- Remove/treat any identified precipitating cause.
- Nothing by mouth 24-48 hours; intravenous fluids.
- Avoid fluid overload (measure central venous pressure or monitor carefully clinically).
- Avoid/treat hypokalemia (triggers hepatic encephalopathy).
- Avoid/treat hypoglycemia (monitor blood glucose every 1 to 2 hours, particularly in small breeds in which hypoglycemia is common and can cause permanent cerebral damage).
- Monitor body temperature, and warm gently as necessary.
- Administer enemas to remove ammonia from colon: warm water, lactulose, or dilute vinegar.
- Instill a neomycin retention enema after the colon is clear and administer ampicillin intravenously.
- Treat any seizures:
  - Carefully rule out "treatable" causes (e.g., electrolyte imbalances, hypoglycemia, hypertension, idiopathic epilepsy).
  - Maintain other intensive care measures (as above).
  - Treat with an anticonvulsant:
    - Propofol boluses (1 mg/kg cats, 3.5 mg/kg dogs) followed by infusions (0.1 to 0.25 mg/kg/minute) usually most effective
    - Phenobarbital may also be used; diazepam of limited efficacy

in acute HE rather than in long-term use because intestinal bacteria tend to become resistant to neomycin. In addition, it is not systemically absorbed and remains within the gastrointestinal tract; it is preferable to use a systemically absorbed antibiotic over the long term to protect against bacteremia. The low dose of metronidazole is given to avert neurotoxicity as a potential adverse effect of delayed hepatic excretion. Other therapeutic strategies investigated in humans with chronic HE include ornithine aspartate supplementation (see Box 39-1) and probiotics to increase numbers of beneficial bacteria. These may show benefit in dogs in the future, but there are currently no published studies documenting their use in small animals.

### **Controlling Precipitating Factors**

Certain conditions are known to accentuate or precipitate HE and should be avoided or treated aggressively when detected (Box 39-3). In fact, in many cases it is the precipitating factors (rather than the diet) that are most important in triggering HE. It is particularly important to identify and treat any concurrent inflammatory disease because even infections as apparently mild as cystitis or middle ear disease can trigger HE episodes in susceptible individuals. Recent work in humans and experimental animals has highlighted the importance of inflammation and inflammatory cytokines in triggering HE (Wright et al., 2007).



BOX 39-3

Precipitating Factors for Hepatic Encephalopathy in a Susceptible Individual

#### Increased Generation of Ammonia in the Intestine

- A high-protein meal (e.g., puppy or kitten food)
- Very poorly digestible protein reaching the colon and allowing bacterial metabolism to ammonia
- Gastrointestinal bleeding (e.g., bleeding ulcer in acquired shunts with portal hypertension) or ingestion of blood
- Constipation (increases contact time between colonic bacteria and feces and therefore increases ammonia production)
- Azotemia (urea freely diffuses across colonic membrane and is split by bacteria to ammonia)

#### **Increased Generation of Ammonia Systemically**

- Transfusion of stored blood
- Catabolism/hypermetabolism/protein-calorie malnutrition (increases breakdown of lean body mass with release of NH<sub>3</sub>)
- Feeding a poor-quality protein (excessive deamination as protein is used for energy)

## Effects on the Uptake and Metabolism of Ammonia in the Brain

- Metabolic alkalosis (increases amount of unionized NH3 in circulation ,which increases passage across blood-brain barrier)
- Hypokalemia (results in alkalosis with consequences outlined above)
- Sedatives/anesthetics (direct interaction with various neurotransmitters)
- Estrus (may be due to production of neurosteroids with neurologic effects)
- Inflammation (inflammatory cytokines have been implicated in having a direct central effect)

#### ACUTE HEPATIC ENCEPHALOPATHY

#### **Treatment**

Acute HE is a true medical emergency. Fortunately, it is much less common than chronic, waxing and waning HE. Animals may present in seizure or comatose, and although HE initially causes no permanent brain damage, prolonged seizures, status epilepticus, or coma will; prolonged severe HE by itself may lead to serious cerebral edema as a result of accumulation of the osmolyte glutamine (from ammonia detoxification) in astrocytes. In addition, the effects of acute HE, particularly hypoglycemia, can be fatal if not recognized and treated. The treatment of acute encephalopathic crises is outlined in Box 39-2. Intensive management is required. However, treatment is worthwhile because some animals can go on to complete recovery and successful long-term medical management, particularly if the acute crisis was triggered by

CHAPTER 39

a definable event (e.g., acute gastrointestinal bleeding in a dog with chronic liver disease and portal hypertension). Nothing by mouth (NPO), administration of enemas, and intravenous fluid therapy constitute the basic therapeutic approach. Warm water cleansing enemas may be useful simply by removing colonic contents and preventing absorption of intestinal encephalotoxins. Lactulose or dilute vinegar may be added to acidify the colon and decrease absorption of ammonia. The most effective enema contains three parts lactulose to seven parts water at a total dose of 20 ml/kg. The solution is left in place, with the aid of a Foley catheter, as a retention enema for 15 to 20 minutes. For lactulose to be beneficial, the pH of the evacuated colon contents must be 6 or lower. These enemas can be given every 4 to 6 hours. Because lactulose is osmotically active, dehydration can occur if enemas are used too aggressively without careful attention to fluid intake. Fluids chosen for replacement of losses, volume expansion, and maintenance should not contain lactate, which is converted to bicarbonate, because alkalinizing solutions may precipitate or worsen HE by promoting formation of the more readily diffusible form of ammonia. Half-strength (0.45%) saline solution in 2.5% dextrose is a good empirical choice, with potassium added according to its serum concentration (see Table 55-1). Serum electrolyte concentrations in dogs with HE are extremely variable; until the results become available, 20 mEq KCl/L in administered fluids is a safe amount to add. Seizuring dogs can be stabilized with low-dose propofol infusions (Fig. 39-2) or phenobarbital. The dose of propofol is calculated by giving an initial bolus to effect (usually about 1mg/kg), timing how long it takes for the animal to show mild signs of seizuring, such as mild limb paddling again, and then dividing the dose by the time to calculate an infusion rate. For example, if after a bolus of 1 mg/kg of propofol the dog began to show signs of seizure activity again after 10 minutes, the infusion rate to give would be 1/10 = 0.1 mg/kg/min. In practice, the dose of propofol to give by constant rate infusion is usually about 0.1 to 0.2 mg/kg/min. Dogs sometimes need to remain on the infusion for hours or days, but the



FIG 39-2
A Miniature Schnauzer with a congenital portosystemic shunt that had postligation seizures is stabilized with a propofol infusion.

rate can be gradually reduced to control seizures while still allowing the dog to regain consciousness—in some cases, even enough to start eating.

In spite of some early promising reports, there is still no convincing evidence in support of other pharmacological treatments for HE, apart from antibiotics and lactulose, and therefore other drugs cannot currently be recommended for use in dogs. Trials of the benzodiazepine receptor antagonist flumazenil in human patients with refractory acute HE have had mixed results, and although flumazenil has been studied in animals for its ability to reverse the action of benzodiazepine tranquilizers, there have been no clinical studies on its use in acute HE in animals.

### **PORTAL HYPERTENSION**

### **Pathogenesis**

Portal hypertension is the sustained increase in blood pressure in the portal system and is seen most frequently in dogs with chronic liver disease, although it may also occasionally occur in dogs with acute liver disease. Portal hypertension is extremely uncommon in cats. It is caused by the increased resistance to blood flow through the sinusoids of the liver or (less commonly) by more direct obstructions to the portal vein such as thromboemboli. Early in chronic liver disease, portal hypertension can be the result of multiplication and phenotypic transformation of hepatic Ito (stellate) cells, which become contractile myofibroblasts that surround the sinusoids and cause constriction. In the longer term, fibrous tissue laid down by these transformed stellate cells results in more irreversible sinusoidal obstruction. The most common cause of portal hypertension is therefore chronic hepatitis progressing to cirrhosis in dogs (Fig. 39-3). It can also occur in association with hepatic neoplasia or diffuse hepatic swelling.

The changes in hemodynamics associated with "back pressure" in the portal circulation result in one or more of the typical triad of intestinal wall edema/ulceration, ascites, and acquired PSSs. Acquired PSSs occur as "escape valves" when the portal vein pressure is consistently higher than the pressure in the caudal vena cava (see Fig. 38-2). They are always multiple and occur as a result of the opening up of previously nonfunctional veloomental vessels. They are an important compensatory mechanism because they dissipate some of the increased portal pressure, limiting the increase in splanchnic pressure and thus reducing the risk of gastrointestinal ulceration. In humans with chronic portal hypertension, acquired PSSs have been demonstrated to prolong life expectancy by reducing the chance of serious gastrointestinal or esophageal bleeding—to the point that if they are not already present, they are often created surgically. Similar survival data are not available for dogs, but it is clear that ligation of acquired PSS is contraindicated and will result in fatal splanchnic congestion. Acquired PSSs result in HE in a similar way to congenital PSSs; treatment is outlined in the preceding section.

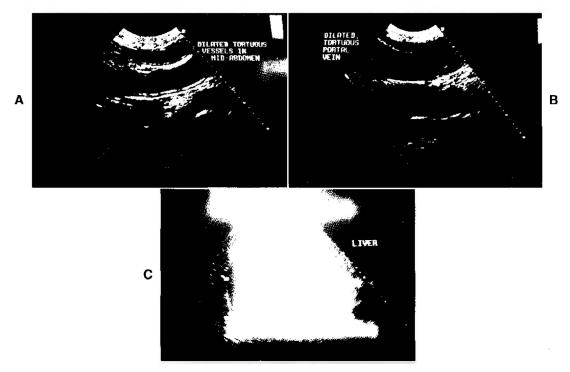


FIG 39-3

Ultrasonographic images demonstrating the progressive development of ascites with portal hypertension in a dog with cirrhosis: Ultrasonography on the first visit showed no evidence of free abdominal fluid, but dilated vessels in the midabdomen (including splenic congestion, A) and also a dilated portal vein (B). When the dog returned for a liver biopsy 2 weeks later, ultrasonography now revealed the development of mild early ascites (C). (Courtesy

Diagnostic Imaging Dept, Queen's Veterinary School Hospital, University of Cambridge.)

# SPLANCHNIC CONGESTION AND GASTROINTESTINAL ULCERATION

### **Pathogenesis**

Splanchnic congestion is a common and early complication of portal hypertension, the result of the pooling of blood in the splanchnic circulation and reduced flow into the portal system (see Fig. 39-3). This can cause visible congestion and edema of the gut wall that can be detected either ultrasonographically (where there may be thickening and loss of layering of the gut) or during surgery. It occurs before the onset of ascites and persists after ascites resolves (see Fig. 39-3). The congested gut wall is at increased risk of GI ulceration. Catastrophic gastrointestinal or esophageal ulceration is the most common cause of death in humans with portal hypertension who do not undergo a liver transplant, and it appears also to be the most common cause of death in dogs with stable chronic liver disease (see Fig. 39-1). Ulceration associated with portal hypertension in humans often takes the form of bleeding esophageal varices, whereas in dogs the ulceration is most commonly in the proximal duodenum, presumably reflecting a difference in the anatomy of the portal system in the two species. Preventing gastrointestinal ulceration is therefore vital, and for this reason it is very important to refrain from using ulcerogenic drugs (e.g., steroids) in dogs with portal hypertension whenever possible.

Corticosteroids have been shown to shorten the life expectancy of humans with chronic hepatitis and concurrent portal hypertension and should not be used in dogs with portal hypertension unless there is a very good reason for it. If they are deemed necessary, the owners should be fully informed of their potentially serious adverse effects. Other triggers for GI ulceration in dogs with portal hypertension are sepsis and protein-calorie malnutrition (discussed in more detail later), particularly if combined with a period of anorexia (see Fig. 39-1). The small intestine requires luminal glutamine and other nutrients to permit effective healing, and prolonged anorexia results in an increased risk of gastrointestinal ulceration as a result of glutamine depletion.

The clinician must be aware that GI ulceration may occur acutely in dogs with splanchic congestion and serious clinical deterioration may occur before melena is apparent because it takes several hours for the blood to pass from the small to the large intestine. Before this occurs, it is possible for the animal to show sudden onset and marked signs of HE because blood is a "high-protein meal" in the small intestine (see preceding section) or even for the ulcer to perforate and cause peritonitis (see Fig. 39-1).

### **Treatment**

Treatment of gastrointestinal ulceration largely revolves around its prevention (i.e., avoiding triggers as much as pos-

sible, such as the use of steroids or nonsteroidal antiinflammatory drugs, and avoiding hypotension during any surgery). It is particularly important that any dog with portal hypertension that undergoes a prolonged period of anorexia is fed because these individuals will be at high risk of gastrointestinal ulceration if they do not receive nourishment (see Fig. 39-1). Parenteral nutrition is not an effective alternative in these dogs because it does not supply luminal nutrients for enterocyte healing (in fact, upper gastrointestinal ulceration is a common adverse effect of total parenteral nutrition in humans, even in those without portal hypertension), and some form of enteral support should be instituted as soon as possible. The use of gastric acid secretory inhibitors (H2 blockers or proton pump inhibitors) is of questionable benefit in patients with portal hypertension because it is usually the duodenum that is ulcerated (rather than the stomach); also, there have been reports that the gastric pH in dogs with liver disease may already be higher than normal as a result of changes in gastrin metabolism. However, in the face of active ulceration and melena, they are often used in the hope that they will help. In these circumstances, cimetidine is contraindicated because of its effect on hepatic P450 enzymes; therefore ranitidine (2 mg/kg administered orally or via slow IV administration q12h) or famotidine (0.5 to 1 mg/kg administered PO q12-24h) are recommended. Likewise, sucralfate (Carafate<sup>TM</sup>.) is of questionable efficacy; it is most effective against gastric ulceration (i.e., in association with a low pH), but it is often used (at a dosage of 500 mg to 1 g per dog PO q8h). Hemostasis profiles should also be evaluated, and any coagulopathy treated with vitamin K (see the section on coagulopathy) or plasma transfusions.

### **ASCITES**

### **Pathogenesis**

The development of ascites (defined as the accumulation of a transudate or modified transudate in the peritoneal cavity) is another consequence of portal hypertension (see Fig. 39-3), but the pathogenesis is complex and has really been studied only in humans; it is assumed that the mechanisms of ascites are similar in dogs. One way in which dogs differ from humans is that dogs do not develop the "spontaneous" infection of ascites of liver origin by extension of gut bacteria into the fluid that results in peritonitis, which is commonly reported in people. The presence of ascites is a poor prognostic indicator in humans with chronic hepatitis, and the same appears to be true in dogs. Hypoalbuminemia contributes to the development of ascites but by itself is rarely sufficient to cause fluid accumulation; portal hypertension is a critical contributing factor. The development of ascites in patients with liver disease also seems to lead to sodium retention by the kidneys. In many cases there is systemic hypotension and increased renal sodium retention, partly as a result of reduced glomerular filtration rate and decreased sodium delivery to the tubules and partly as a result of increased release of renin-angiotensin-aldosterone (RAAS) that results in increased sodium retention in the distal

tubules. This leads to an increase in circulating fluid volume, precipitating the formation of ascites, which in turn reduces venous return because of increased pressure on the caudal vena cava and initiates a vicious cycle of renal sodium retention and ascites. Therefore aldosterone antagonists are usually most effective in dogs with ascites secondary to portal hypertension, whereas loop diuretics, such as furosemide used alone, can be ineffective or even, in some cases, actually increase the volume of effusion by causing a further decrease in systemic blood pressure as a result of hemoconcentration and secondary increases in RAAS activation.

#### **Treatment**

Treatment of ascites associated with liver failure revolves around the use of diuretics: first aldosterone antagonists (spironolactone, 1 to 2 mg/kg administered PO q12h), but then with the addition of furosemide (2-4 mg/kg administered PO q12h) if necessary in refractory cases. Spironolactone usually takes 2 or 3 days to reach full effect, and the resolution of ascites can be monitored by weighing the patient daily (any acute changes in weight will be due to fluid shifts). Dietary sodium restriction has also been recommended, although it is unclear how effective or important this is. However, it is certainly wise to refrain from feeding the patient high-salt snacks and treats.

It is very important to monitor serum electrolyte concentrations (mainly sodium and potassium) daily during the first few days of treatment and every few weeks to months thereafter, depending on how stable the dog and drug doses are. Hypokalemia should be avoided because it can precipitate HE (see preceding section), but it is less likely in a dog on both aldosterone antagonists and loop diuretics than in a dog on furosemide alone. Hyponatremia can also occur; if it is marked, the diuretics should be stopped and the patient given careful intravenous replacement until the sodium is normalized.

Therapeutic paracentesis is indicated only in patients with ascites that is severe enough to compromise breathing. This is actually unusual and is manifested by severe, drumlike ascites; the dog is unable to settle and lie down. Paracentesis should be accompanied by concurrent intravenous administration of a colloid plasma expander, plasma, or albumin; removal of a large volume of fluid containing albumin can result in a precipitous hypoalbuminemia and decrease in oncotic pressure, leading to pulmonary edema. This is a real problem in dogs with chronic liver disease in which the liver's capacity to manufacture albumin is reduced. Clear recommendations for dogs have not been published, but the recommendations for humans, adapted for dogs, are outlined in Box 39-4.

#### COAGULOPATHY

#### **Pathogenesis**

The liver plays a central role in both the coagulation and fibrinolytic systems. The liver synthesizes all the coagulation



BOX 39-4

Guidelines for Therapeutic Paracentesis in Dogs with Ascites Resulting from Liver Disease

Reserve for use ONLY in cases with severe, refractory ascites:

- Small volume paracentesis: follow up with intravenous plasma expansion with 2 to 5 ml/kg of gelofuscin or hemaccel
- Large volume paracentesis: volume expand preferably with albumin using 8 g albumin/l of ascites removed (i.e., 100 ml of 20% albumin per 3 liters of ascites).
   Failing that, use fresh frozen plasma (10 ml/kg slowly)

Adapted from Moore et al: Guidelines on the management of ascites in cirrhosis, *Gut* 55 (suppl 6):vi1, 2006.

factors with the exception of factor VIII and also makes the inhibitors of coagulation and fibrinolysis. Factors II, VII, IX, and X also require hepatic activation by a vitamin Kdependent carboxylation reaction. Hemostatic abnormalities are quite common in both dogs and cats with liver disease; in one study 50% and 75% of dogs with liver disease had prolongation of the one-stage prothrombin time (OSPT) and activated partial thromboplastin time (APTT), respectively (Badylak et al., 1983). In another study 82% of cats with liver disease had hemostatic abnormalities (Lisciandro et al., 1998). Cats appear to be particularly susceptible to prolongation of clotting times; this is at least partly due to reduced vitamin K absorption. Dogs and cats with vitamin K-responsive coagulopathies have prolongation of both the OSPT and APTT (and the OSPT may actually be longer than the APTT). Vitamin K is a fat-soluble vitamin, and its absorption is decreased in association with biliary tract disease (which is common in cats); bile acid secretion into the small intestine is also reduced. Moreover, the inflammatory bowel disease commonly seen concurrently in cats with chronic biliary tract disease results in reduced fat absorption. Finally, some cats with chronic biliary tract disease have concurrent chronic pancreatitis, and as this progresses to exocrine pancreatic insufficiency, fat absorption (and thus vitamin K absorption) will decline further.

In contrast, dogs with chronic liver disease rarely have clinically relevant prolongation of clotting times. However, in both species severe diffuse liver disease, particularly acute infiltration such as lipidosis (cats) and lymphoma (cats and dogs), will cause a decrease in the activity of clotting factors in many cases as a result of hepatocyte damage and reduced synthesis in the liver. In patients with lymphoma or lipidosis this decreased activity of clotting factors is rapidly reversible if the underlying disease can be successfully treated, thus allowing recovery of hepatocyte function. In one study of cats coagulopathies were seen most commonly in cats with hepatic lipidosis and cats with inflammatory bowel disease and concurrent cholangitis (Center et al., 2000).

Coagulopathies can also occur in dogs and cats with liver disease as a result of disseminated intravascular coagulation (DIC) with resultant prolongation of clotting times and thrombocytopenia. DIC is particularly a complication of acute, fulminating hepatitis and also some hepatic tumors; it carries a very poor prognosis.

### **Clinical Features and Diagnosis**

Despite the presence of hemostatic abnormalities, spontaneous bleeding is uncommon in patients with chronic liver disease but relatively common in those with acute disease. Because dogs with portal hypertension and gastrointestinal hemorrhage (see previous section) may also have a coagulopathy predisposing to their bleeding, they should be thoroughly evaluated. However, the risk of hemorrhage increases after a challenge to hemostasis, such as liver biopsy; therefore it is very important to evaluate hemostasis before performing liver biopsy. One study (Bigge et al., 2001) suggested that thrombocytopenia was a more significant predictor of bleeding complications after ultrasonography-guided biopsies in dogs and cats than prolongation of the OSPT and APTT. Therefore clinicians must perform a platelet count in dogs and cats before performing a liver biopsy. A platelet estimate can be can be done manually on the blood smear (Chapter 87) The platelet count (per  $\mu$ L) can be estimated by counting the number of platelets in 10 oil immersion fields and multiplying the average number per field by 15,000 to 20,000. Prolongation of coagulation times may also increase the risk of bleeding; in the same study, prolongation of the OSPT in dogs and the APTT in cats was significantly associated with bleeding complications after biopsy. Ideally, therefore, both OSPT and APTT should be evaluated in cats and dogs before hepatic biopsy; however, a practical alternative could be assessment of at least an activated clotting time (ACT) in a glass tube containing diatomaceous earth as a contact activator, although theoretically this is more useful in cats than dogs because it assesses the intrinsic pathway (=APTT) and final common pathway only.

Because factor depletion must be greater than 70% to result in prolongation of the OSPT or APTT, many more dogs and cats may have subtle abnormalities in the concentration of individual coagulation factors. These can be detected by more sensitive tests, such as measuring the concentration of individual clotting factors or the PIVKA (proteins induced by vitamin K absence) test, although its clinical efficacy in large numbers of dogs and cats is untested. If available, thromboelastography may allow for rapid quantification of hemostasis (see Chapter 87).

In dogs and cats with severe acute liver disease, spontaneous bleeding may result from depletion of clotting factors; in addition, there is a potential for developing DIC (see Chapter 87). In patients with DIC, APTT and OSPT may be prolonged, but it is impossible to distinguish this from reduced hepatic production of clotting factors. However, measurement of increased D-dimers and/or fibrin degradation products, combined with decreases in platelet count, increases the index of suspicion for DIC. D-dimer concen-

trations are often mildly to moderately increased in dogs with liver disease because of reduced clearance in the liver, and this does not necessarily mean that the dog has a thrombus or DIC. More marked elevations are suggestive of DIC.

#### **Treatment**

Dogs and cats with prolonged clotting times associated with chronic liver disease often respond to parenteral vitamin K supplementation alone. It is recommended that all patients receive vitamin K1 (phytomenadione), at a dosage of 0.5 to 2.0 mg/kg administered IM or SQ 12 hours before biopsy and repeated q12h for 3 days as necessary.

It is important to monitor clotting during long-term therapy (OSPT + APTT or PIVKA) and stop when they normalize because it is possible to overdose on vitamin K, which can result in Heinz body hemolysis. If the coagulopathy fails to respond to vitamin K treatment alone or if there are clinical signs of hemorrhage associated with the disease (which is more common with acute disease), administration of fresh frozen plasma or stored plasma is indicated to replenish depleted clotting factors. A starting dose of 10 ml/kg given slowly is recommended; the dose of plasma is titrated on the basis of the results of the OSPT and APTT. Again, liver biopsy, surgery or the placement of central venous catheters should not be contemplated until coagulation times have been normalized.

The treatment of DIC is difficult and frequently unsuccessful. The most effective treatment is to remove the inciting cause, which in acute liver failure in humans means rapid liver transplant. Without this option in dogs and cats, the mortality in DIC of acute fulminant hepatitis is likely to be 100%. Recommended therapies include plasma transfusion to replace depleted clotting factors and careful heparin therapy during the hypercoagulable phase. However, the efficacy of heparin therapy in DIC has recently been called into question in humans, and there are no clinical data supporting its use in dogs and cats.

### PROTEIN-CALORIE MALNUTRITION

### **Pathogenesis**

Protein-caloric malnutrition is very common in dogs with chronic hepatitis as a result of reduced intake caused by anorexia, vomiting, and diarrhea and increased loss/wastage of calories caused by hypermetabolism and poor liver function. Protein-caloric malnutrition is likely to have a serious impact on both longevity and quality of life in affected dogs. There are no studies specifically addressing the effect of malnutrition on survival and infections of dogs with liver disease, but in other canine diseases it is known to increase the risk of septic complications. This is true in humans with portal hypertension and also likely in dogs. In humans with portal hypertension malnutrition also predisposes to gut ulceration. In addition, negative nitrogen balance and reduced muscle mass predispose to HE. Breakdown of body protein results in more ammonia production, and also in a normal

individual up to 50% of arterial ammonia is metabolized in skeletal muscle by conversion of glutamate to glutamine, so loss of muscle mass will reduce the ability to detoxify ammonia. What gives the most cause for concern regarding protein-calorie malnutrition in the veterinary patient is that it is often partly caused by well-meaning but unhelpful manipulations by the clinician or even by a lack of recognition and attention (discussed in greater detail later). For this reason, it is very important that clinicians treating dogs with chronic liver disease remain alert to the possibility of protein-calorie malnutrition.

Malnutrition can also be seen in dogs and cats with congenital PSS, both as a result of reduced liver synthetic capability or as a result of inappropriately severe protein restriction by the attending clinician. Cats with chronic liver disease may have negative energy balance, often as a result of the effects of concurrent intestinal and pancreatic disease reducing digestion and absorption of food. In addition, cats in negative nitrogen balance are at a particular risk of developing acute hepatic lipidosis (see Chapter 37) so protein-calorie malnutrition in this species requires particularly aggressive management.

### **Clinical Signs and Diagnosis**

When suffering from severe malnutrition, dogs and cats appear cachectic, with reduced muscle mass. However, loss of muscle mass occurs relatively late in the process, and in the earlier stages of protein-calorie malnutrition the animal's body condition score may be normal and yet many potentially deleterious effects on the immune system and gut wall will already be under way. There is no simple blood test that allows diagnosis of malnutrition. The most effective means to do this is by taking a careful history as well as performing a clinical examination. Any animal with liver disease should be considered as being at risk of protein-calorie malnutrition. A history of partial or complete anorexia for more than 3 days or recent weight loss of >10% not associated with fluid shifts should trigger rapid and aggressive nutritional management.

### **Treatment**

The treatment is to feed the patient an appropriate diet. Protein restriction should be avoided as much as possible—and in some cases of chronic liver disease associated with obvious cachexia, supplementation of a maintenance diet with extra high-quality protein (such as dairy protein) is even indicated. If the patient will not eat voluntarily, some form of assisted tube feeding should be instituted short term. This is particularly important in cats with hepatic lipidosis, which almost invariably refuse to eat independently and require gastrostomy or esophagostomy tube feeding (see Chapter 37). A search should then be made for any underlying cause of anorexia, such as concurrent infections (see Fig. 39-1).

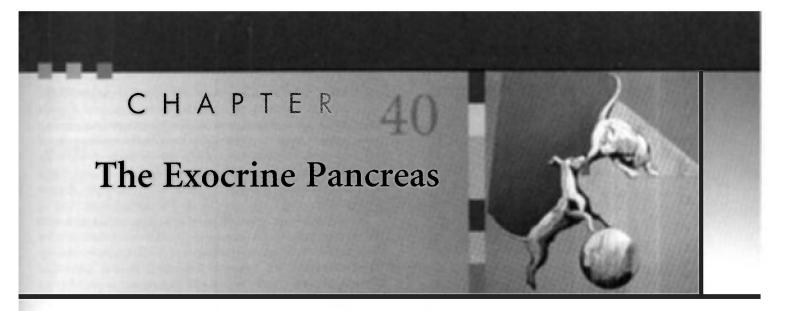
It is very important to avoid iatrogenic malnutrition while the patient is hospitalized. Withholding food for several days to allow multiple tests (e.g., liver biopsy or endoscopy) is a common problem; tests should be spread out over a

longer period if necessary to allow feeding between them. It is also possible for malnutrition to develop unnoticed in the hospital as a result of inadequate record keeping and frequent staff turnover. Finally, feeding an excessively protein-restricted diet to a dog or cat with liver disease can also result in negative nitrogen balance.

### Suggested Readings

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### CHAPTER OUTLINE

GENERAL CONSIDERATIONS PANCREATITIS

Acute Pancreatitis
Chronic Pancreatitis
EXOCRINE PANCREATIC INSUFFICIENCY
EXOCRINE PANCREATIC NEOPLASIA
PANCREATIC ABSCESSES, CYSTS, AND
PSEUDOCYSTS

### **GENERAL CONSIDERATIONS**

The pancreas is located in the cranial abdomen, with the left limb positioned between the transverse colon and the greater curvature of the stomach and the right limb running alongside the proximal duodenum. Any or all of these neighboring structures can be affected when there is pancreatic inflammation. The exocrine acini make up about 90% of pancreatic tissue, and the endocrine islets interspersed among the acini make up the other 10% (Fig. 40-1). The close anatomical association between the acini and islets allows subtle signaling between them to coordinate digestion and metabolism, but it also means that there is a complex cause-and-effect relationship between diabetes mellitus and pancreatitis. The major function of the exocrine pancreas is to secrete digestive enzymes, bicarbonate, and intrinsic factor (IF) into the proximal duodenum. Pancreatic enzymes are responsible for the initial digestion of larger food molecules and require an alkaline pH to function (hence the concurrent bicarbonate secretion by pancreatic duct cells). The pancreas secretes several proteases, phospholipases, ribonucleases, and deoxyribonucleases as inactive precursors (zymogens) and also -amylase and lipase as intact molecules. The pancreas is the only significant source of lipase, and hence steatorrhea (fatty feces) is a prominent sign of exocrine pancreatic insufficiency (EPI). Trypsin is central to the pathogenesis of pancreatitis, as outlined in the subsequent sections, and

inappropriate early activation of the zymogen trypsinogen to trypsin within the pancreatic acini is the final common pathway triggering pancreatic inflammation. In the normal animal pancreatic secretion is triggered by the thought of food and stomach filling and most potently by the presence of fat and protein in the small intestinal lumen. The vagus nerve, the local enteric nervous system, and the hormones secretin and cholecystokin from the small intestine all stimulate pancreatic secretion. Trypsinogen is activated within the small intestine by the brush border enzyme enterokinase, which cleaves a peptide (the "trypsin-activation peptide" [TAP]) from trypsinogen. Activated trypsin then activates the other zymogens within the intestinal lumen. IF, which is necessary for vitamin B<sub>12</sub> absorption in the ileum, is secreted only by the pancreas in the cat. In the dog the pancreas is the main source of IF, but a small amount is also secreted by the gastric mucosa.

Diseases of the exocrine pancreas are relatively common but often misdiagnosed in both dogs and cats because of nonspecific clinical signs and a lack of sensitive and specific clincopathological tests. Pancreatitis is the most common disease of the exocrine pancreas in both cats and dogs; EPI, although less common, is also recognized frequently. Uncommon diseases of the pancreas include pancreatic abscess, pseudocyst, and neoplasia.

Recent advances in the understanding of the pathophysiology, prevalence, and potential causes of pancreatitis in dogs and cats may give clues to treatment in the future, although treatment of acute pancreatitis remains largely nonspecific and supportive in all species.

Important differences in the anatomy of the pancreas and associated areas between the dog and cat are outlined in Table 40-1.

### **PANCREATITIS**

Pancreatitis may be acute or chronic. As with acute and chronic hepatitis, the difference is histological and not necessarily clinical (Table 40-2 and Fig. 40-2), and there is some clinical overlap between the two. Chronic disease may present

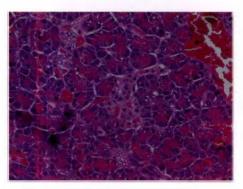


FIG 40-1
Histopathology of a section of normal canine pancreas showing two paler staining islets of Langerhans and exocrine acini surrounding them. Note that the islets make up only 10% to 20% of the volume of the pancreas.

initially as an acute-on-chronic episode; in postmortem studies of fatal acute pancreatitis in dogs and cats, up to half of the cases were actually acute-on-chronic disease. Differentiation of truly acute disease from an acute flare-up of chronic disease is not important for initial management, which is the same in all cases, but is important to allow recognition of the potential long-term sequelae of chronic disease, as outlined in the following sections. The causes of acute and chronic pancreatitis may be different, but there may also be some overlap between them.

### **ACUTE PANCREATITIS**

### **Etiology and Pathogenesis**

Understanding of the pathophysiology of acute pancreatitis in humans has increased in recent years with the discovery of hereditary mutations of trypsin, which predispose to pancreatitis; the pathophysiology of this disease is believed to be similar in dogs and cats. The final common pathway in all cases is the inappropriate early activation of trypsinogen within the pancreas as a result of increased autoactivation and/or reduced autolysis. Trypsin is the major protease secreted by the pancreas, and inappropriate early activation within the acinar cells would obviously cause autodigestion and severe inflammation. Protective mechanisms therefore exist to prevent early activation: Trypsin is stored within zymogen granules in the pancreatic acini as the inactive precursor trypsinogen; up to 10% of trypsinogen gradually autoactivates within the granules but is inactivated by the action of other trypsin molecules and by the co-segregating protective molecule pancreatic secretory trypsin-inhibitor (PSTI; also known as serine protease inhibitor Kazal type 1, or SPINK1). Genetic mutations of trypsinogen, which make it resistant to hydrolysis, and/or of PSTI predispose to pancreatitis in people and are also likely to occur in some dogs (Table 40-3). If too much trypsin autoactivates within the pancreas, the protective mechanisms are overwhelmed and a chain reaction occurs, whereby activated trypsin activates more trypsin and the other enzymes within the pancreas, with the resulting pancreatic autodigestion, inflammation, and peripancreatic fat necrosis that leads to focal or more generalized sterile peritonitis. There is an associated systemic inflammatory response (SIR) in even the mildest cases of pancreatitis. Many other organs may be involved, and in the most severe cases, there is multiorgan failure and diffuse intravascular coagulation (DIC). The circulating protease inhibitors  $\alpha_l$ -antitrypsin (=  $\alpha_l$ -protease inhibitor) and  $\alpha$ -macroglobulin play a role in removing trypsin and other proteases from the circulation. Saturation of these protease inhibitors by excessive amounts of circulating proteases contributes to the systemic inflammation, but generalized neutrophil activation and cytokine release is probably the primary cause of SIR.

The previous paragraph describes the final common pathway of acute pancreatitis in dogs and cats, but the underlying cause of the disease is often unknown (see Table 40-3). There appears to be a strong breed relationship in dogs with pancreatitis, so hereditary causes are likely to be a factor in this species. Many of the previously reported supposed causes in dogs are likely triggers for disease in genetically susceptible individuals.

#### **Clinical Features**

Acute pancreatitis typically affects middle-aged dogs and cats, although very young and very old individuals may also be affected. Terrier breeds, Miniature Schauzers, and domestic short-haired cats appear to be at increased risk for acute pancreatitis, although any breed or cross-breed can be affected. Some dog breeds appear to be underrepresented in clinical studies, particularly large and giant breeds, although Labrador Retrievers are sometimes affected and also sometimes Husky-types (particularly in Australia). Breed relationships suggest an underlying genetic tendency, mirroring the situation in humans. It is likely that the disease is multifactorial with a genetic tendency and superimposed triggering factors. For example, eating a high-fat meal may be a trigger for a susceptible terrier. Some studies suggest a slight increase in risk in female dogs, whereas others show no sex predisposition. Obesity has been suggested as a predisposing factor in dogs, but it is unclear whether this is a cause or whether it is co-segregating with disease (i.e., breeds at high risk for acute pancreatitis may coincidentally also be breeds with a high risk for obesity). In cats there is a recognized association with concurrent cholangitis, inflammatory bowel disease, or renal disease in some cases. Cats with acute pancreatitis are also at high risk for hepatic lipidosis.

The history in dogs often includes a trigger such as a high-fat meal or engorging (see Table 40-3). Recent drug therapy may also be a trigger, particularly potassium bromide, azathioprine or asparaginase in dogs. Concurrent endocrine diseases such as hypothyroidism, hyperadrenocorticism, or diabetes mellitus (DM) increase the risk of severe fatal pancreatitis in dogs; therefore it is important to identify these in the history. In cats the history may include features of concurrent cholangiohepatitis, inflammatory bowel disease, or hepatic lipidosis (or any combination thereof).



TABLE 40-1

Differences in Pancreatic Structure, Function, and Diseases Between Dogs and Cats

FEATURE	DOGS	CATS
Anatomy	Usually two pancreatic ducts:	Usually single major pancreatic duct joining the
(but many variations; some dogs are like	large accessory duct from right limb to minor papilla in duodenum	common bile duct before entering duodenum at duodenal papilla 3 cm distal to pylorus
cats and vice versa)	small pancreatic duct from left limb to major duodenal papilla in duodenum beside (but not joining) bile duct	20% of cats have second, accessory duct; occasionally ducts remain separate Sphincter of Oddi may be as important as in
	Sphincter of Oddi unlikely to be of clinical significance	humans
Pancreatic function	Intrinsic factor secreted largely by pancreas but also some in stomach; vitamin B <sub>12</sub> deficiency common in exocrine insufficiency but sometimes normal	Intrinsic factor secreted entirely by pancreas so Vitamin B <sub>12</sub> deficiency very common in exocrine insufficiency; vitamin K deficiency also common because of concurrent liver and intestinal disease further reducing absorption
Pancreatitis: disease associations	Common association between pancreatitis and endocrine disease (see text)	Common association with cholangiohepatitis and/or inflammatory bowel disease
	Association with liver and small intestinal disease not recognized	High risk concurrent hepatic lipidosis May also be associated with renal disease
	Emerging association in some breeds with immune-mediated diseases, particularly keratoconjunctivitis sicca (see text)	may also be associated with retial disease
Exocrine pancreas: other pathology	Incidental pancreatic nodular hyperplasia common	Incidental pancreatic nodular hyperplasia common
. •	Cystic acinar degeneration rare	Cystic acinar degeneration common and associated with chronic pancreatitis
Pancreatitis: spectrum of disease	Most cases acute at presentation Low-grade chronic disease increasingly	Most cases low-grade, chronic interstitial, and a challenge to diagnose
	recognized and more common than acute on postmortem studies	Acute severe cases also recognized
Pancreatitis: diagnosis	Histology gold standard	Histology gold standard
· ·	Variety of catalytic and immunoassays available	Catalytic assays no help Immunoassays more helpful
	Ultrasonography quite sensitive	Ultrasonography less sensitive than in dogs
	Obvious/suggestive clinical signs in acute cases	Clinical signs usually low-grade and nonspecific even in acute disease
Causes of exocrine pancreatic insufficiency	Often pancreatic acinar atrophy— increased prevalence in certain breeds (especially German Shepherd Dogs)	Most cases end-stage chronic pancreatitis Pancreatic acinar atrophy not reported
,	End-stage chronic pancreatitis also common and under-recognized, particularly middle-aged to older dogs of specific breeds (see text)	

The clinical signs in dogs vary with the severity of the disease from mild abdominal pain and anorexia at one end of the spectrum to an "acute abdomen" and potential multiorgan failure and DIC at the severe end of the spectrum. Dogs with severe acute disease usually present with acute vomiting, anorexia, marked abdominal pain, and varying degrees of dehydration, collapse, and shock. The vomiting is initially typical of delayed gastric emptying resulting from peritonitis, with emesis of undigested food a long time after feeding progressing to vomiting only bile. The main differential diagnoses in these cases are other

causes of acute abdomen, particularly intestinal foreign body or obstruction; the vomiting may be so severe that the dog may undergo an unnecessary laparotomy for a suspected obstruction if a careful workup was not performed first. Some patients may show the classic "praying stance," with the forelegs on the floor and the hindlegs standing (Fig. 40-3), but this is not pathognomonic for pancreatitis and can be seen in association with any pain in the cranial abdomen, including hepatic, gastric, or duodenal pain. By contrast, cats with severe, fatal, necrotizing pancreatitis usually have surprisingly mild clinical signs, such as anorexia



**TABLE 40-2** 

### Differences Between Acute and Chronic Pancreatitis in Dogs and Cats

	ACUTE PANCREATITIS	CHRONIC PANCREATITIS
Histopathology	Varying degrees of acinar necrosis, edema, and inflammation with neutrophils and peri-pancreatic fat necrosis	Characterized by lymphocytic inflammation and fibrosis with permanent disruption of architecture
	Potentially completely reversible with no permanent pancreatic architectural or functional changes	Possible to have acute-on-chronic cases with concurrent neutrophilic inflammation and necrosis
Clinical appearance	Spectrum from severe and fatal (usually necrotizing) to mild and subclinical (less common)	Spectrum from mild, low-grade intermittent gastrointestinal signs (most common) to an acute-on-chronic episode indistinguishable from classical acute pancreatitis
Diagnostic challenge	Higher sensitivity of enzyme tests and ultrasonography than in chronic disease	Lower sensitivity of enzyme tests and ultrasonography than in acute disease: diagnosis much more challenging
Mortality and long- term sequelae	High immediate mortality but no long-term sequelae	Low mortality except acute-on-chronic bouts High risk of eventual exocrine and endocrine insufficiency



TABLE 40-3

### Causes of Acute Pancreatitis in Dogs and Cats

RISK FACTOR	CAUSE
Idiopathic 90%	Unknown (some may be hereditary)
Duct obstruction ± hypersecretion ± bile reflux into pancreatic duct	Experimental; neoplasia; surgery ± cholangitis + role in chronic pancreatitis
Hypertriglyceridemia	Inherent abnormal lipid metabolism (breed related, e.g., Min. Schnauzers)
	Endocrine: diabetes mellitus, hyperadrenocortism, hypothyroidism
Breed/sex?	Increased risk terriers ± spayed females—may reflect risk of
	hypertriglyceridemia (also Min. Schnauzers; see above)
Diet	Dietary indiscretion/high-fat diet
	Malnutrition; Obesity?
Trauma	Road traffic accident, surgery, "high rise syndrome"
Ischemia/reperfusion	Surgery (not just pancreas), gastric dilatation and volvulus; shock, severe immune-mediated hemolytic anemia (common association if anemia severe)
Hypercalcemia	Experimental; hypercalcemia of malignancy (uncommon association clinically); primary hyperparathyroidism
Drugs/toxins	Organophosphates; azathioprine; asparaginase; thiazides; furosemide; estrogens; sulpha drugs; tetracycline; procainamide, potassium bromide.
Infections	Toxoplasma, others (uncommon)

From Villiers E, Blackwood L, editors: BSAVA manual of canine and feline clinical pathology, ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.

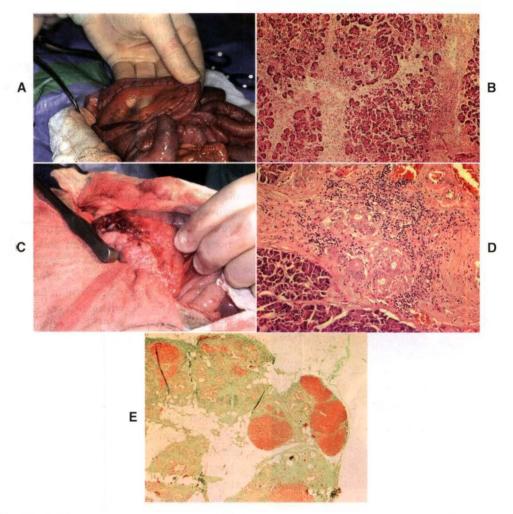
and lethargy; vomiting and abdominal pain occur in fewer than half the cases.

At the milder end of the spectrum, dogs and cats may present with mild gastrointestinal signs—typically anorexia and sometimes some mild vomiting, followed by the passage of some colitic-like feces accompanied by some fresh blood resulting from local peritonitis in the area of the transverse colon. Inflammatory bowel disease, low-grade infectious enteritis, and chronic hepatitis would be major differential diagno-

ses for this presentation in dogs as well as cats. Animals that are still eating may show prominent postprandial discomfort.

Both cats and dogs with acute pancreatitis can present with jaundice, either at initial examination or often developing a few days later, when the initial acute signs are resolving. In fact, most, if not all, animals with jaundice have acute-onchronic disease (see the section on chronic pancreatitis).

Careful clinical examination should focus on identification of the degree of dehydration and shock, careful assess-



#### FIG 40-2

A, Gross appearance of acute pancreatitis in a cat at laparotomy demonstrating generalized hyperemia. It is also possible for acute pancreatitis to appear normal grossly. B, Histopathological appearance of acute pancreatitis in a young adult female West Highland White Terrier. Note prominent edema and inflammation disrupting the acini. This case was fatal, but it would have been potentially completely reversible if the dog had survived the acute phase. Hematoxylin and eosin ×100. C, Gross appearance of chronic pancreatitis in a middle-aged Jack Russell Terrier. Note nodular appearance of pancreas and extensive adhesions to the duodenum obscuring the mesentery. It is also possible for chronic pancreatitis to appear normal grossly. D, Histological appearance of chronic pancreatitis from a 10-year-old male Cavalier King Charles Spaniel. Note fibrosis, mononuclear inflammatory cells, and ductular hyperplasia. Hematoxylin and eosin ×200. E, Histological appearance of end-stage chronic pancreatitis in an 11-year-old neutered female Cavalier King Charles Spaniel with diabetes mellitus and exocrine pancreatic insufficiency. Note extensive fibrosis (green) and small islands of remaining acini (red). Massons Trichrome ×40. (A and C, From Villiers E, Blackwood L, editors: BSAVA manual of canine and feline clinical pathology, ed 2, Gloucestershire, United Kingdom, 2005, British Small Animal Veterinary Association.)

ment for any concurrent diseases (particularly endocrine disease), and careful abdominal palpation. In severe cases petechiae or ecchymoses suggestive of DIC may be identified, and there may be respiratory distress associated with acute respiratory distress syndrome. Careful clinical and clinicopathological assessment of the degree of shock and concurrent organ damage is important for prognosis

and treatment decisions, as outlined in the following sections. Abdominal palpation should identify pancreatic pain and rule out, if possible, any palpable foreign bodies or intussusceptions, although abdominal imaging will be required to rule these out with confidence. In severe cases generalized peritonitis will result in generalized unmistakable abdominal pain, whereas in milder cases careful palpation of the cranial

abdomen is required to identify a focus of abdominal pain, as indicated in Fig. 40-4. Occasionally, a cranial abdominal mass may be palpated, particularly in cats, representing a focus of fat necrosis.

### **Diagnosis**

### **Routine Clinical Pathology**

Routine laboratory analysis (i.e., complete blood count [CBC], serum biochemical profile, and urinalysis) typically does not help in arriving at a specific diagnosis, but it is very important to perform these in all but the mildest cases because they give important prognostic information and aid in effective treatment, as outlined in the following sections.



PIG 40-3
Dog exhibiting evidence of cranial abdominal pain by assuming the "position of relief." (Courtesy Dr. William E. Hornbuckle, Cornell University, College of Veterinary Medicine.)

Typical clinicopathologic abnormalities in dogs and cats with acute pancreatitis are shown in Table 40-4.

### **More Specific Pancreatic Enzyme Assays**

More specific laboratory tests for the pancreas are the catalytic assays amylase and lipase and the immunoassays trypsinlike immunoreactivity (TLI) and pancreatic lipase immunoreactivity (PLI). Catalytic assays rely on the ability of the molecule to catalyze a reaction in vivo and thus rely on presence of active enzyme; however, they are not species specific. In cats amylase and lipase are of very questionable diagnostic value. Immunoassays, however, use an antibody against a part of the enzyme molecule distant from the active site and thus will also measure inactive precursors (e.g., trypsinogen) and tend to be organ and species specific. The advantages and disadvantages of the different assays are outlined in Table 40-5. Overall, PLI has the highest sensitivity and likely the highest specificity in both species and is the only reliable test for pancreatitis currently available in cats. A SNAP® test for canine PLI has recently been released by IDEXX (see details at http://www.idexx.com/animalhealth/ testkits/snapcpl/index.jsp), which should aid in rapid diagnosis.

### **Diagnostic Imaging**

The most sensitive way to image the canine and feline pancreas noninvasively is by ultrasonography. Abdominal radiographs in patients with pancreatitis usually show mild or no changes, even in those with severe disease (Fig. 40-5). However, in patients with acute disease, abdominal radiography plays an important role in ruling out acute intestinal obstruction, which would result in obvious changes, primarily dilated, gas-filled, stacking loops of intestine. Classical radiographic changes in dogs and cats with acute pancreatitis include focal decrease in contrast in the cranial abdomen



FIG 40-4

Carefully palpating a Cocker Spaniel for cranial abdominal pain. **A,** The clinician should palpate craniodorsally under the rib cage for evidence of focal pancreatic pain (as shown in this dog by turning of the head). **B,** With deep-chested dogs it helps to ask an assistant to elevate the head of the dog to displace the pancreas caudally (effectively achieving the opposite of the dog in Fig. 40-3).



**TABLE 40-4** 

### Typical Clinicopathologic Findings in Dogs and Cats with Acute Pancreatitis

PARAMETER	CHANGES IN DOGS	CHANGES IN CATS	CAUSE AND SIGNIFICANCE
Urea +/- creatinine	Increased in 50% to 65% of cases	Urea increased in 57% of cases and creatinine in 33%	Usually prerenal because of dehydration and hypotension (urea > creatinine) and indicates need for aggressive fluid therapy Often also some intrinsic renal failure (sepsis and
Potassium	Decreased in 20% of cases	Decreased in 56% of cases	immune-complexes) Increased loss in vomiting and renal loss with fluid therapy + reduced intake and aldosterone release caused by hypovolemia Requires treatment because contributes to gastrointestinal atony
Sodium	Can be increased (12%), decreased (33%), or normal	Usually normal or decreased (23%) Increased only in 4% of cases	Increase caused by dehydration; decrease caused by loss in gastrointestinal secretions with vomiting
Chloride	Very commonly decreased (81%)	Unknown	Loss in gastrointestinal secretions with vomiting
Calcium	Increased in about 9% of cases and decreased in about 3% of cases	Total calcium reduced in 40% to 45% of cases; ionized calcium reduced in 60% of cases; total calcium increased in 5%	Reduction poor prognostic indicator in cats but of no prognostic significance in dogs; caused by saponification in peripancreatic fat (unproven) and glucagon release stimulating calcitonin in some. Increased calcium likely cause rather than effect of disease
Phosphate	Often increased (55%)	Increased in 27%, decreased in 14%	Increase usually due to reduced renal excretion secondary to renal compromise; decrease (in cats) due to treatment for diabetes mellitus
Glucose	Increased in 30% to 88%, decreased in up to 40%	Increased in 64%, very rarely decreased	Increased because of decreased insulin and increased glucagon, cortisol, and catecholamines; about half return to normal; decreases caused by sepsis and anorexia
Albumin	Increased in 39% to 50%, reduced in 17%	Increased in 8% to 30%, reduced in 24%	Increase due to dehydration; decrease due to gut loss, malnutrition, concurrent liver disease, or renal loss
Hepatocellular enzymes (ALT and AST)	Increased in 61%	Increased in 68%	Hepatic necrosis and vacuolation due to sepsis, local effects of pancreatic enzymes +/- concurrent hepatic disease in cats
Cholestatic enzymes (ALP and GGT)	Increased in 79%	Increased in 50%	Biliary obstruction due to acute-on-chronic pancreatitis +/- concurrent cholangitis +/- lipidosis in cats; steroid induced ALP in dogs
Bilirubin	Increased in 53%	Increased in 64%	As GGT
Cholesterol	Increased in 48% to 80%	Increased in 64%	Can be due to cholestasis; unclear in others if cause or effect: often due to concurrent/ predisposing disease
Triglycerides	Commonly increased	Rarely measured	Unclear if cause or effect: often due to concurrent/ predisposing disease
Neutrophils	Increased in 55% to 60%	Increased in about 30%, decreased in 15%	Increase due to inflammatory response; decrease in some cats due to consumption—may be poor prognostic indicator
Hematocrit	Increased in about 20% and decreased in about 20%	As dogs	Increase due to dehydration; decrease due to anemia of chronic disease; gastrointestinal ulceration
Platelets	Commonly decreased in severe cases (59%)	Usually normal	Decrease due to circulating proteases +/- disseminated intravascular coagulation

Data from Schaer M: A clinicopathological survey of acute pancreatitis in 30 dogs and 5 cats, *J Am Anim Hosp Assoc* 15:681, 1979; Hill RC et al: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat: a retrospective study of 40 cases (1976-1989), *J Vet Intern Med* 7:25, 1993; Hess RS, et al: Clinical. Clinicopathological, radiographic and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986-1995), *J Am Vet Med Assoc* 213:665, 1998; Mansfield CS et al: Review of feline pancreatitis. Part 2: clinical signs, diagnosis and treatment, *J Feline Med and Surgery* 3:125, 2001.



**TABLE 40-5** 

The Use of Specific Catalytic Enzyme Tests and Immunoassays in the Diagnosis of Acute and Chronic Pancreatitis in Dogs and Cats

ASSAY	ADVANTAGES	DISADVANTAGES
Catalytic assays Dogs only—of no use in cats		Either may be normal in severe ± chronic pancreatitis due to enzyme depletion ± loss of tissue; degree of elevation of no prognostic value, except where stated; both renally excreted and elevated 2 or 3 times in azotemia
Amylase	Widely available on in-house analyzers Steroids do not elevate it so can help diagnose pancreatitis in dog with hyperadrenocorticism	Low sensitivity and specificity because of high background level from other sources, including small intestine
Lipase	Widely available on practice analyzers; more sensitive than amylase; degree of elevation may have prognostic significance	Extrapancreatic sources so high background level. Steroids elevate up to 5×.
Immunoassays		
Canine TLI •	Elevations high specificity for pancreatitis	Low sensitivity for diagnosis of pancreatitis (but high sensitivity for EPI); said to rise and fall more quickly than lipase or amylase; renally excreted: elevated 2 or 3 times in azotemia May be inappropriately low in severe ± chronic cases
		due to pancreatic depletion ± loss of tissue mass; no clear prognostic significance
Feline TLI	One of only two assays available for cats	Lower sensitivity and specificity than canine TLI—better used for diagnosis of EPI; renally excreted so elevated in azotemia
Canine PLI	Early indications most sensitive and specific test for canine pancreatitis; organ specific, so no interference from extrapancreatic sources  Now available as in-house test	Increased in renal disease but may not be significantly so? (Unclear yet if affected by steroids)
	(see URL in text)	
Feline PLI	Very new test but appears most sensitive and specific test available for feline pancreatitis	Very little published data available on its use

TU, Trypsinlike immunoreactivity; PU, pancreatic lipase immunoreactivity

associated with local peritonitis; a dilated, fixed (C-shaped), and laterally displaced proximal duodenum on ventrodorsal views; and caudal displacement of the transverse colon. Occasionally, a "mass" effect may be seen in the region of the pancreas, usually the result of fat necrosis. Pancreatic tumors by contrast are usually small, but it is impossible to differentiate fat necrosis from neoplasia using imaging alone. Abdominal radiographs appear normal in many dogs and cats with acute or chronic pancreatitis. Barium studies should be avoided, if possible, because they do not contribute to diagnosis and the associated gut filling provides further stimulus for pancreatic enzyme release.

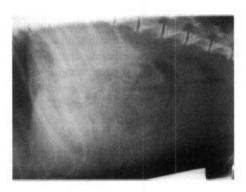
The most sensitive imaging modalities in humans with pancreatitis are magnetic resonance imaging (MRI), computed tomography (CT), or transendoscopic ultrasonography. CT has so far proved disappointing in both cats and

dogs. Pancreatic MRI has not been reported in small animal species, and transendoscopic ultrasonography is not widely available, although it would be expected to be useful insofar as the pancreas can be imaged very closely from the adjacent stomach or duodenum. Because all these techniques require general anesthesia, they may never become widely used in small animal patients with severe acute pancreatitis. Transcutaneous ultrasonography has a high specificity for pancreatic disease (i.e., if a lesion is found, it is real) but a variable sensitivity depending on the skill of the operator and the severity of the disease. Ultrasonography has a higher sensitivity for classical acute pancreatitis in both dogs and cats because associated edema and peripancreatic fat necrosis result in visible interfaces. The sensitivity is much lower for chronic pancreatitis in both cats and dogs (Fig. 40-6).

# Fluid Analysis

Some dogs and cats with pancreatitis have abdominal effusion. Fluid analysis usually reveals serosanguineous sterile exudates, although transudates and chylous effusions have also been reported in cats. Amylase and lipase activities in the fluid may be higher than in the serum, and elevated lipase in the effusion can be diagnostically helpful (Guija de Arespacochaga et al., 2006). Pleural effusions also occur in a small number of dogs with acute pancreatitis as a result of generalized vasculitis.

The search continues for the ideal diagnostic test for pancreatitis. Trypsin-activation peptide (TAP) is well conserved between species, so human ELISAs can be used for dogs and



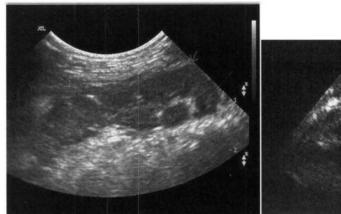
#### FIG 40-5

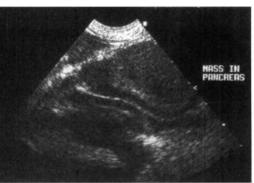
Lateral abdominal radiograph from a 7-year-old Jack Russell Terrier with acute pancreatitis. There are minimal changes apparent apart from a mild loss of abdominal contrast, in spite of the severity of the disease. This does, however, help to rule out acute obstruction because the intestinal loops are not dilated and gas filled. (Courtesy the Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge.)

cats. However, elevations in either plasma or urine TAP are no more sensitive or specific than currently available blood tests. In dogs the best prognostic indicator is the modified organ score, as shown in Tables 40-6 and 40-7. This system has been extrapolated from humans, but its use as a prognostic and treatment indicator in cats has not been critically evaluated. Of the individual diagnostic tests, the following were found to be negative prognostic indicators in dogs: high urinary TAP: creatinine ratio, marked increases in serum lipase activity, marked increases in serum creatinine and phosphate concentrations, and low urine specific gravity. In cats, the following negative prognostic indicators were found: low ionized calcium and leukopenia. Urinary or plasma TAP do not appear to be prognostically useful in cats, and neither does the degree of elevation of TLI in either species. The prognostic significance of degree of elevation of cPLI activity is currently unknown.

# Histopathology

Definitive diagnosis of acute pancreatitis can be achieved only via histopathology of a pancreatic biopsy, but this is invasive and not indicated in most cases. However, if the animal has a laparotomy during its investigation, the clinician should always remember to visually inspect the pancreas and also, preferably, to obtain a small biopsy. The pancreas usually appears grossly inflamed and may have a masslike appearance. The latter is usually due to fat necrosis and/or fibrosis and not neoplasia; therefore no animal should be euthanized on the basis of a tumorlike appearance in the pancreas without supportive cytology or pathology because most large masses in the pancreas are not tumors. As in the small intestine, it is possible for the pancreas to appear grossly normal despite having clinically relevant disease, particularly in cats and in dogs and cats with low-grade chronic





В

# FIG 40-6

**A,** Typical ultrasonographic appearance of acute pancreatitis in a Miniature Schnauzer with a diffusely hypoechoic pancreas *(white arrows)* with surrounding hyperechoic mesentery. **B,** Typical ultrasonographic appearance of chronic pancreatitis in an English Cocker Spaniel. There is a masslike effect displacing the duodenum. Many dogs and cats with chronic pancreatitis have an unremarkable abdominal ultrasound. (Courtesy the Diagnostic Imaging Department, Queen's Veterinary School Hospital, University of Cambridge.)

disease. Pancreatic biopsy is safe and does not carry a high risk of postoperative pancreatitis, provided that the pancreas is handled gently and the blood supply is not disrupted. It is best to take a small biopsy from the tip of a lobe and not to ligate any vessels, particularly on the right limb, which shares a blood supply with the proximal duodenum.

However, in most cases a biopsy will not be performed and diagnosis is based on a combination of clinical suspicion, specific enzyme tests, and diagnostic imaging. No one non-invasive test is 100% sensitive and specific for pancreatitis in dogs and cats; in a few cases of even severe disease, all the tests may be negative.

# **Treatment and Prognosis**

The treatment and prognosis of dogs and cats with acute pancreatitis depends on the severity of the condition at presentation. Severe acute pancreatitis is a very serious disease, has a very high mortality, and requires intensive management, whereas more moderate disease can be managed with intravenous fluids and analgesia, and patients with mild disease can sometimes be managed on an outpatient basis.

The easiest and most practical way to scale treatment and prognosis in dogs is to use the organ-scoring system modified from human medicine by Ruaux and Atwell (1998) and Ruaux (2000; see Tables 40-6 and 40-7). Cats, even those with severe disease, are more difficult to assess because of their mild clinical signs and because the utility of the organ-scoring system has not yet been assessed in this species. It therefore seems prudent to assume that all cats have severe disease unless proved otherwise and treat them intensively, with the intent of preventing hepatic lipidosis and other fatal complications.

The inciting cause of the pancreatitis should be treated or removed in the few cases where it is known (e.g., hypercalcemia or drug-induced), and every effort should be made during treatment to avoid further potential triggers, as outlined in Table 40-3. Most cases of pancreatitis are, however, idiopathic, and treatment is largely symptomatic. The one



TABLE 40-6

Modified Organ Scoring System for Treatment and Prognostic Decisions in Acute Pancreatitis

SEVERITY AND DISEASE SCORE*		PROGNOSIS	EXPECTED MORTALITY %
Mild	0	Excellent	0
Moderate	1	Good to fair	11
	2	Fair to poor	20
Severe	3	Poor	66
	4	Grave	100

<sup>\*</sup> The severity scoring system is based on the number of organ systems apart from the pancreas showing evidence of failure or compromise at initial presentation; see Table 40-7 for details on scoring. This scoring system was developed for acute pancreatitis in dogs. It is unclear whether this system can be applied to cats or to acute-on-chronic pancreatitis in dogs.

From Ruaux CG et al: A severity score for spontaneous canine acute pancreatitis, Austr Vet J 76:804, 1998; and Ruaux CG: Pathophysiology of organ failure in severe acute pancreatitis in dogs, Compend Cont Edu Small Anim Vet 22:531, 2000.



**TABLE 40-7** 

Criteria to Assess Organ System Compromise for Severity Scoring System in Canine Acute Pancreatitis

ORGAN SYSTEM	CRITERIA FOR COMPROMISE	LAB REFERENCE RANGE
Hepatic	One or more of alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase >3× upper reference range	
Renal	Blood urea >84 mg/dl	Blood urea 15-57 mg/dl
	Creatinine >3.0 mg/dl	Creatinine 0.6-1.8 mg/dl
Leukocytic	>10% band neutrophils or total white cell count >24 × 103/µl	Band neutrophils 0.0-0.2 × 103/µl Total white cell count 4.5-17 × 103/µl
Endocrine pancreas*	Blood glucose >234 mg/dl and/or β-OH butyrate >1 mmol/l	Blood glucose 59-123 mg/dl β-OH butyrate 0.0-0.6 mmol/l
Acid/base buffering*	Bicarbonate <13 or >26 mmol/l and/or anion gap <15 or >38 mmol/l	Bicarbonate 15-24 mmol/l Anion gap 17-35 mmol/l

<sup>\*</sup> If increased glucose, butyrate, and acidosis co-exist, count as one system.

From Ruaux CG et al: A severity score for spontaneous canine acute pancreatitis, Austr Vet J 76:804, 1998.

exception is chronic pancreatitis in English Cocker Spaniels, which may be an immune-mediated disease in which steroids and other immunosuppressive drugs may be indicated as a specific treatment (see the section on chronic pancreatitis for more details). Occasionally, Cocker Spaniels with chronic pancreatitis present with acute clinical signs, and judicious corticosteroid therapy might be considered in these individuals. However, there is no evidence that corticosteroid therapy helps in other breeds of dogs, including terriers, and in these the use of such drugs might actually worsen prognosis by increasing the risk of gastric ulceration and reducing the activity of the reticuloendothelial system in the removal of circulating \alpha\_2-macroglobulin-protease complexes. In some instances, a dog or cat may need corticosteroid therapy for a concurrent condition, such as immune-mediated hemolytic anemia or inflammatory bowel disease, in which case the benefits of corticosteroids may outweigh their potential deleterious effects.

Severe, necrotizing pancreatitis (scores 3 and 4; Tables 40-6 and 40-7) carries a poor to very poor prognosis in both cats and dogs. These patients have severe fluid and electrolyte abnormalities associated with systemic inflammatory disease, renal compromise, and a high risk of DIC. Intensive management is required, including plasma transfusions in many cases and enteral tube feeding or total parenteral nutrition in some (see next section). These patients will likely benefit from referral to a specialist. If referral is not an option, intensive therapy can be attempted in the practice, but the owner must be warned of the very poor prognosis and expense of treatment.

At the other end of the spectrum, patients with very mild pancreatitis (score 0) may simply need hospitalization for 12 to 24 hours of intravenous fluid therapy if they are vomiting and dehydrated; if they are alert and well-hydrated, they may be managed at home with 24 to 48 hours of pancreatic rest (fluids only by mouth) and analgesia followed by long-term feeding of an appropriate diet.

It is important to give consideration to the following aspects of treatment in all patients: intravenous fluid and electrolyte replacement; analgesia; nutrition; and other supportive therapy, as indicated, such as antiemetics and antibiotics.

# Intravenous Fluids and Electrolytes

Intravenous fluid therapy is very important in all but the mildest cases of pancreatitis to reverse dehydration, address electrolyte imbalances associated with vomiting and fluid pooling in the hypomotile gastrointestinal tract, and maintain adequate pancreatic circulation. It is vital to prevent pancreatic ischemia associated with reduced perfusion because it contributes to necrosis. Replacement fluids (e.g., lactated Ringer's or Plasmalyte) are usually used at rates and volumes that depend on the degree of dehydration and shock—twice maintenance (100 to 120 ml/kg/day) rates are adequate for mild to moderately affected animals (grades 0 and 1), but more severely affected animals may need initial shock rates (90 ml/kg/hour for 30 to 60 minutes) followed

by synthetic colloids. It is important to measure urine output concurrently. Rapid crystalloid infusion in severely affected animals that have a pathological increase in vascular permeability carries an increased risk of pulmonary edema, so patients should be closely monitored; central venous pressure ideally should be measured in the most severely affected dogs.

Serum electrolyte concentrations should be carefully monitored. Potential electrolyte abnormalities are outlined in Table 40-4, but the most clinically important abnormality in most cases is hypokalemia caused by vomiting and reduced food intake. Hypokalemia can significantly impair recovery and contribute to mortality because it causes not only skeletal muscle weakness but also gastrointestinal atony, which will contribute to the clinical signs of the disease and delay successful feeding. Aggressive fluid therapy further increases renal potassium loss, particularly in cats, so it is important to measure serum potassium concentrations frequently (at least daily while the patient is vomiting) and add supplemental potassium chloride to the fluids as necessary. A scaled approach is best, based on the degree of hypokalemia. Lactated Ringer's or Plasmalyte contains only 4 mEq/l potassium, and most cases require supplementing at least to replacement rates (20 mEq/l). Even if serum potassium concentration cannot be measured, a vomiting anorexic dog with no evidence of renal failure should receive replacement rates of potassium in the fluids. More severely hypokalemic dogs should be supplemented more, as long as serum concentrations can be regularly measured and infusion rates carefully controlled. A dog or cat with a serum potassium concentration of 2.0 mEq/l or less should receive between 40 and 60 mEq/l in the fluids at a controlled infusion rate. As a general rule, the infusion rate of potassium should still not be increased above 0.5 mEq/kg/hour.

A plasma transfusion is indicated in dogs and cats with severe pancreatitis (organ score 2 to 4) to replace  $\alpha_1$ -antitrypsin and  $\alpha_2$ -macroglobulin. It also supplies clotting factors and may be combined with heparin therapy in animals at high risk of DIC, although the efficacy of heparin therapy in DIC in humans and animals has recently been questioned and there are no controlled trials that either support or refute its use in pancreatitis in dogs and cats at present.

# **Analgesia**

Pancreatitis is usually a very painful condition in humans and animals. Hospitalized patients should therefore be monitored carefully for pain, and analgesia should be administered as necessary. In practice, analgesia is indicated in almost all patients with pancreatitis and should be given routinely to cats with pancreatitis because pain is difficult to assess in this species. Morphine agonists or partial agonists are often used, particularly buprenorphine. Morphine, meperidine, and fentanyl (intravenous or patches) can also be used (Table 40-8). Concerns that the effects of opiates on the sphincter of Oddi might exacerbate disease have often been cited with regard to dogs as well as humans, but more recent studies



TABLE 40-8

	INDICATIONS AND	DOSE AND	DOSE AND	
ANALGESIC	CAUTIONS	ROUTE: DOGS	ROUTE: CATS	NOTES
Buprenorphine	Most generally useful analgesic in hospitalized case Cats (but not dogs) may be dosed orally at home	IV, SC, IM: 0.01- 0.02 mg/kg	IV, SC, IM as dogs Orally in cats (Robertson et al., 2003)	Concerns about effects on Sphincter of Oddi largely unfounded
Butorphanol	Authors have very limited experience of its use—other opiates preferred in acute pancreatitis because of butorphanol's cardiovascular effects (see notes)	0.05-0.6 mg/kg IM, SC, or IV q6-8h; 0.1-0.2 mg/kg/h as a CRI Oral: 0.5-1 mg/kg q6-12h	As dogs	At analgesic doses in humans it increases pulmonary artery pressure and cardiac work, unlike the other analgesics in the table, so other opiates preferred
Meperidine (Demerol)	Meperidine by injection only, hence hospitalized animals NOT for IV administration	5 mg/kg SC, IM q2h	3-5 mg/kg SC, IM q2h	Painful on injection Is derived from atropine and therefore, in contrast to the other opioids, is a spasmolytic agent on smooth muscle—might be useful for the gut
Methadone	Little nausea or vomiting so more useful than morphine	0.2-0.4 mg/kg SC or IM q4-6h or as required	0.2 mg/kg SC or IM q4-6h or as required	Can produce dysphoria
Hydromorphone	•	0.05 mg/kg IV q4h; 0.1-0.4 mg/kg IM	0.1 mg/kg IM q7h	Can produce dysphoria
Fentanyl patches	Very useful, care with home discharge	2-4 μg/kg/h patch	25 μg/h patch with half exposed	24-hour onset and 72-hour duration in dogs; 7-hour onset and 72-hour duration in cats
Tramado <b>l</b>	Authors have no personal experience of using this in acute pancreatitis but may be a useful drug for home use orally for mild to moderate pain.	Oral: 2-5 mg /kg q8-12h	Oral: 2-4 mg/ kg q 8-12 h	Tramadol also decreases cardiac contractility; shoul not be used in acute phas when myocardial depressal factor may be released. No published studies on pharmacokinetics in small animals so doses empirical Dysphoria more likely in car
Ketamine infusion	Severe refractory pain in hospitalized patient	2 μg/kg/min	As dogs	Useful as adjunct, probably not suitable as sole analgesic; can produce dysphoria at higher infusion rates
Lidocaine infusion	Excellent analgesic for hospitalized patients	Bolus of 1 mg/kg IV followed by 20 µg/kg/min infusion	0.1 mg/kg/h	Use with caution in cats because of lidocaine toxicity
Acetaminophen (Paracetamol)	Mainstay nonsteroidal in human pancreatitis; often neglected in dogs, but useful because it does not have the same deleterious effects on the gastrointestinal tract and kidneys	10 mg/kg orally q12h	DO NOT USE as is toxic	Should not be used if significant concurrent liver disease

**TABLE 40-8** 

Details of Analgesics Used on Acute Pancreatitis—cont'd

ANALGESIC	INDICATIONS AND CAUTION	DOSE AND S ROUTE: DOGS	DOSE AND ROUTE: CATS	NOTES
Carprofen and other nonsteroidal antiinflammatory drugs	with great care because of potential gut and renal	Carprofen: 4 mg/kg SC, IV, or orally q24h; maintain on 2 mg/kg q12h	Carprofen: 2 mg/kg SC, IV, or orally; maintain on 2 mg/kg	Underestimated efficacy COX 1:2 inhibition ratio of 65

(With thanks to Dr. Jackie Brearley, Senior Lecturer in Veterinary Anaesthesia, the Queen's Veterinary School Hospital, University of Cambridge, UK.)

have suggested minimal clinically relevant effects, except when high and repeated doses of morphine are used; these drugs are regularly used now in humans with pancreatitis with no obvious problems. Fentanyl patches take time to achieve effect (on average, 24 hours in dogs and 7 hours in cats), so concurrent use of an opiate for the first few hours after application is recommended. Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided if possible because of the increased risk of gastroduodenal ulceration in patients with pancreatitis and also the potential of some NSAIDs to precipitate renal failure in animals with hypotension and/or shock. In people acute pancreatitis has been associated with the use of NSAIDs. Cyclo-oxygenase-2 inhibitors have a lower risk ratio than the conventional NSAIDs in this respect. Alternative analgesics that could be considered in severe cases include a low-dose intravenous ketamine infusion, which has the advantage of minimal effect on gastrointestinal motility (Bares et al., 1995) or intravenous lidocaine. Details of analgesia are given in

Providing analgesia that can be dispensed for the client to take home in patients with milder or resolving disease can be a challenge. The pain should not be underestimated in these patients. However, it is difficult to find effective and safe analgesia that can be dispensed for use at home. Administration of opioids during visits to the clinic is wise, and one of the less ulcerogenic NSAIDs could be used cautiously at home. Cats can be effectively dosed with buprenorphine orally (Robertson et al., 2003), allowing simple home medication, but the oral route is not effective in dogs. Anecdotally, Tramadol has been found to be helpful in dogs. Feeding a low-fat diet helps reduce postprandial pain in humans and anecdotally helps some dogs significantly. However, administering pancreatic enzymes in the food does not seem to reduce pain in dogs, and there is little evidence in support of their use for pain relief in either dogs or cats.

# **Nutrition**

It is very important to consider appropriate nutritional management of the patient with pancreatitis. Complete pancreatic rest by starvation, avoiding anything by mouth (including water or barium), has traditionally been advised for patients with acute pancreatitis. Initially, it was believed that early enteral nutrition was contraindicated because it was likely to result in cholecystokinin and secretin release, with consequent release of pancreatic enzymes and worsening of pancreatitis and associated pain. Total parenteral nutrition (TPN) seemed a more logical route early in the disease process, with jejunal tube feeding later in the disease aiming to bypass the areas of pancreatic enzyme stimulation. However, recent studies have suggested that early enteral nutrition is preferable to TPN, and current best practice in human medicine is outlined in Box 40-1 along with relevance to veterinary patients. It is no longer appropriate or acceptable to starve the patient for days and days while awaiting resolution of disease. Increasing evidence is accumulating in human medicine of the importance of early enteral nutrition in patients with pancreatitis, and emerging work in humans suggests that immunomodulating nutrients may also be of benefit. There are no studies evaluating the efficacy of early or late enteral or parental nutrition in naturally occurring pancreatitis in dogs or cats. Therefore the advice currently given is based on anecdotal evidence, extrapolation from humans, and on experimental studies in dogs only.

However, early feeding of an appropriate diet is now indicated in dogs. In addition, starvation is contraindicated in cats because of the high risk of hepatic lipidosis. The current advice is therefore to institute some form of enteral feeding, whenever possible, within 48 hours in both dogs and cats. The more severe the disease, the more important it is to feed early. In severe cases this is best achieved with jejunostomy tube feeding by continuous infusion of an elemental diet,

IV, Intravenous; SC, subcutaneous; IM, intramuscular.



BOX 40-1

# Best Practice for Feeding Patients with Acute Pancreatitis

Recent studies and metaanalyses of studies of nutrition in human acute pancreatitis have led to changes in advice for best-practice feeding in these cases (Meier and Beglinger, 2006). Note that early enteral nutrition is **particularly** indicated in severe disease, which is perhaps unexpected and counter to our current practice in dogs.

- A negative nitrogen balance is common in acute pancreatitis and is associated with a tenfold increase in mortality, although there have been no studies looking at association of disease severity with nitrogen balance. This is also likely to be true in small animals but has not been specifically investigated.
- IV feeding of glucose, protein, or lipids does not stimulate pancreatic secretions. However, whether feeding is IV or enteral, blood glucose should be kept normal because hypoglycemia or hyperglycemia is associated with a negative outcome. Insulin is used if the patient becomes hyperglycemic on feeding, but this should be done only carefully in an intensive care situation with regular (hourly) monitoring of blood glucose.
- Intrajejunal infusion of elemental diets in humans and experimental canine models of pancreatitis does not stimulate pancreatic enzyme release significantly.
- Early oral feeding after acute pancreatitis in humans is associated with increased pain, whereas jejunal feeding is not. This has not been assessed in small animals.
- Important: early intrajejunal feeding is preferred over total parenteral nutrition in patients with acute pancreatitis, particularly severe disease.
   Results of metaanalysis in humans show that intrajejunal feeding after 48 hours significantly reduced incidences of infections, reduced surgical interventions, and reduced length of hospital stay and cost over total parenteral nutrition. These findings have also been replicated in dogs with

- experimental acute pancreatitis but not yet in clinical pancreatitis in dogs, although the experiences from early enteral feeding in other gastrointestinal diseases in this species, such as parvovirus enteritis (Mohr et al., 2003), suggest that the recommendations may be similar. Most recently, it has been suggested that feeding may even be given safely intragastrically in humans with acute pancreatitis, although more studies are needed to confirm this.
- Type of diet used: In humans, elemental diets have been used in most cases and usually by continuous infusion. No studies have really assessed whether less elemental diets would also work. Recent studies looking at immune-modulating micronutrients in the diets, such as glutamine, fiber, arginine, omega-3 fatty acids, and probiotic bacteria, have been encouraging (Pearce et al., 2006), but more studies are needed before definite conclusions can be drawn. No similar studies have been undertaken in dogs and cats.
- In mild acute pancreatitis in humans current best practice is to withhold food in many cases for a little longer. Fluids, electrolytes, and analgesics are delivered for 2 to 5 days, and then a diet rich in carbohydrate and moderate in fat and protein is initiated with discharge on a normal diet within 4 to 7 days. Again, there are no specific recommendations for mild acute disease in dogs and cats.
- In cats: Current anecdotal recommendations are to feed immediately in mild, moderate, and severe pancreatitis, preferably via a jejunostomy tube, although again it has been suggested that gastrostromy tubes with multiple low-volume feeds should also be safe. There is just one case report of using an endoscopically placed J-tube in a cat with acute pancreatitis (Jennings et al., 2001). The emphasis on early feeding in cats comes from the risk of hepatic lipidosis.

although frequent small-volume feeds of a low-fat food via a gastrostomy tube is also well tolerated in most dogs and cats with moderate pancreatitis. A good initial choice is baby rice mixed with water followed by a low-fat proprietary veterinary diet (such as Eukanuba Intestinal Formula; Hill's i/d; Royal-Canin-Waltham Digestive low fat or Purina Enformula) (Fig. 40-7). Concurrent antiemetics are also essential to allow effective feeding in many cases (see next section). In patients in which enteral nutrition is not possible or when only a small percentage of the daily caloric requirements can be given enterally, some form of supplemental parenteral nutrition should be considered. This is most practically administered as peripheral parenteral nutrition (see Chandler et al., 2000).

# **Antiemetics**

Antiemetics are often necessary to manage acute vomiting in dogs and cats with pancreatitis. Metoclopramide has been used successfully in dogs with pancreatitis (0.5 to 1 mg/kg,

administered intramuscularly, subcutaneously, or orally three times a day, or 1 to 2 mg/kg, administered intravenously over 24 hours as a slow infusion), but its effect on stimulating gastric motility may increase pain and pancreatic enzyme release in some animals. A phenothiazine antiemetic such as chlorpromazine may be more effective in some patients, but phenothiazines have sedative and hypotensive effects, which may be particularly marked if they are used together with opioid analgesia, so care should be taken in these cases. 5-HT3 receptor antagonists such as ondansetron are useful in other forms of vomiting in dogs (such as chemotherapy-induced emesis) but are best avoided in pancreatitis because they have occasionally been reported to trigger pancreatitis in humans. The newly available NK<sub>1</sub> receptor antagonist maropitant, licensed for use in dogs, has both central and peripheral antiemetic effects and is showing promise as an antiemetic in dogs with pancreatitis, although it is not licensed for use in cats. (Maropitant is available as Cerenia (Pfizer) in either an injectable solution (10 mg/ml)



Baby rice is a good first choice for feeding dogs with acute pancreatitis because it contains no fat and protein. It comes as a finely ground rice powder (A) that can then be mixed with water and, if desired, a gravy substitute such as Bovril to enhance the flavor for feeding (B).

or tablets (16 mg, 24 mg, and 60 mg). The dose of injection is 1 mg/kg (i.e., 1 ml per 10 kg body weight once a day for up to 5 days). The dose of the tablets is 2 mg/kg once a day for up to 5 days.

# Gastroprotectants

Patients with acute pancreatitis have an increased risk of gastroduodenal ulceration caused by local peritonitis; they should be monitored carefully for evidence of this (melena, hematemesis) and treated as necessary with sucralfate and acid secretory inhibitors (H<sub>2</sub> blockers such as cimetidine, famotidine, ranitidine, or nizatidine or the proton pump inhibitor omeprazole). Cimetidine should be avoided in animals with concurrent liver disease because of its effect on the cytochrome P450 system. Ranitidine can be used instead in these animals, but its additional gastric prokinetic effect can cause vomiting in some individuals; it should be discontinued if this occurs. Because famotidine does not have these prokinetic effects, it may be preferable.

## **Antibiotics**

Infectious complications are reportedly rare in dogs and cats with pancreatitis, but when they occur, they can be serious; antibiotic therapy has been shown to improve survival in such cases in humans. It is therefore advisable to use broadspectrum antibiotics in dogs and cats with acute pancreatitis because it is not always possible to assess the occurrence or risk of septic complications. Fluroquinolones or potentiated sulphonamides have been used in humans because they penetrate the pancreas well and are effective against most human bacterial isolates from this region. However, because potentiated sulphonamides are potentially hepatotoxic, they are best avoided if there is concurrent hepatic involvement; fluroquinolones are effective against only aerobes, so combination with another antibiotic with action against anaerobes, such as metronidazole or amoxicillin, may be necessary. Metronidazole has the added benefit of being beneficial if there is concurrent inflammatory bowel disease or small intestinal bacterial overgrowth secondary to intestinal ileus.

# Treatment of Biliary Tract Obstruction Associated with Pancreatitis

Most cases of extrahepatic biliary obstruction secondary to acute-on-chronic pancreatitis resolve with conservative management, and surgical or needle decompression of the gallbladder and stenting of the bile duct are usually unnecessary in dogs and cats. In humans it has now been demonstrated that there is no advantage to surgical intervention in most patients and no difference in the severity and chronicity of secondary liver disease between those treated medically and those treated surgically, provided the jaundice resolves within a month (Addallah et al 2007). No such study has been done in small animals, so treatment advice has to be empirical: If the feces remain colored (not white or acholic, which implies complete biliary obstruction) and the jaundice gradually resolves over a week to 10 days, then surgical intervention is not indicated and conservative management with antioxidants and ursodeoxycholic acid are advised (see Chapters 37 and 38).

# **CHRONIC PANCREATITIS**

# **Etiology and Pathogenesis**

Chronic pancreatitis is defined as "a continuing inflammatory disease characterized by the destruction of pancreatic parenchyma leading to progressive or permanent impairment of exocrine or endocrine function or both." The gold standard for diagnosis is histology (see Fig. 40-2), but this is rarely indicated or performed in dogs or cats. Noninvasive diagnosis is difficult with the currently available diagnostic imaging, and blood tests have a lower sensitivity than for acute disease.

Chronic pancreatitis has been considered a rare and not particularly important disease in dogs, whereas it is recognized as the most common form of pancreatitis in cats. However, the early literature published on canine pancreatic disease in the 1960s and 1970s recognized it as a common disease of clinical significance. It was noted that a high proportion of cases of EPI in dogs were caused by chronic

pancreatitis and also that it might be responsible for up to 30% or more of cases of diabetes mellitus (DM). More recent pathological and clinical studies in both dogs (Newman et al., 2004; Watson et al., 2007) and cats (DeCock et al., 2007) have reconfirmed it as a common and clinically relevant disease in both dogs and cats. It is likely to cause intermittent and/or ongoing recurrent gastrointestinal signs and epigastric pain in a high number of dogs and cats, but it is frequently underrecognized because of the difficulty of obtaining a noninvasive diagnosis. In dogs the postmortem prevalence of chronic pancreatitis is up to 34%, particularly in susceptible breeds, and even in studies of fatal acute pancreatitis, acute-on-chronic disease accounts for 40% of cases. In cats an even higher postmortem prevalence of chronic pancreatitis of 60% has been reported. It must be noted that postmortem studies tend to overestimate the prevalence of chronic diseases, which leave permanent architectural changes in the organ, whereas the prevalence of acute, totally reversible diseases will be underestimated, unless the animal dies during the episode. Nevertheless, it is clear that there are many more cases of chronic pancreatitis in veterinary practice than currently recognized and that a number of these are clinically relevant.

# **Idiopathic Chronic Pancreatitis**

As in acute pancreatitis, the cause of chronic pancreatitis in dogs is usually unknown (see Table 40-3). Any age or breed of dog can be affected, but the most typical signalment is a middle-aged to old dog, particularly a Cavalier King Charles Spaniel, Cocker Spaniel, Collie, or Boxer in the U.K. (Watson et al., 2007; Fig. 40-8). The breed prevalence in the U.S. has not been investigated, but an independent large study of EPI in the U.K. found an increased prevalence in older Cavalier King Charles Spaniels, supporting this breed association. Other parts of the world have also reported a high incidence in arctic-type breeds such as Huskies. There is likely to be some overlap with acute disease, although



FIG 40-8
An 8-year-old neutered male English Cocker Spaniel with chronic pancreatitis.

some cases will have a separate etiology. Some cases may represent chronic relapsing cases of acute disease, but many cases are truly chronic from the outset, with an initial mononuclear infiltrate. Genetic causes are likely to be important in dogs, which explains the increased risk in certain breeds.

No particular breed prevalence has been reported for cats with chronic pancreatitis, and domestic shorthairs are most commonly affected.

# **Autoimmune Chronic Pancreatitis**

The particular form of chronic pancreatitis recognized in English Cocker Spaniels in the U.K. is thought to be an autoimmune disorder (Watson et al., 2006b; see Fig. 40-8). As in human autoimmune pancreatitis, it typically affects middle-aged to older dogs, with a higher prevalence in males, and at least 50% of affected dogs subsequently develop DM, EPI, or both. Dogs also often have other concurrent autoimmune disease, particularly keratoconjunctivitis sicca. There is often a mass-like lesion on ultrasound (see Fig. 40-6, B), and biopsies show a typical perilobular diffuse fibrotic and lymphocytic disease centered on perilobular ducts and vessels, with loss of large ducts and hyperplasia of smaller ducts. Immunohistochemistry shows a preponderance of duct and vein-centered CD3+ lymphocytes (i.e., T-cells). The human disease is believed to be a duct-centered immune reaction and responds to steroid therapy, including a reduction in insulin requirement in some diabetics. This is clearly differentiated from the proposed autoimmunity in young German Shepherd Dogs with pancreatic acinar atrophy, which is acinar-centered and does not result in DM (discussed in more detail later). There are not yet any controlled trials evaluating the use of immunosuppressive drugs in English Cocker Spaniels with chronic pancreatitis, but there is now enough circumstantial evidence to justify their use in this particular breed. However, the clinician should note that this is very breed specific; terriers in the U.K., for example, have a very different histopathological and clinical picture of disease that does not appear to be autoimmune, and the use of steroids in terriers with chronic pancreatitis is not recommended.

# **Clinical Features**

Dogs with chronic pancreatitis, regardless of the cause, most commonly present with mild intermittent gastrointestinal signs. Typically, they have bouts of anorexia, occasional vomiting, mild hematochezia, and obvious postprandial pain, which often goes on for months to years before a veterinarian is consulted. The trigger for finally seeking veterinary attention is often an acute-on-chronic bout or the development of DM or EPI. The main differential diagnoses in the low-grade cases are inflammatory bowel disease and primary gastrointestinal motility disorders. Dogs may become more playful and less picky with their food when they are switched to a low-fat diet, which suggests that they previously had postprandial pain. Chronic epigastric pain is a hallmark of the human disease and is sometimes severe enough to lead

to opiate addiction or surgery, so it should not be overlooked or underestimated in small animal patients. In more severe, acute-on-chronic cases, the dogs are clinically indistinguishable from those with classical acute pancreatitis (see preceding section), with severe vomiting, dehydration, shock, and potential multiorgan failure. The first clinically severe bout tends to come at the end of a long (often years) subclinical phase of quietly progressive and extensive pancreatic destruction in dogs. It is very important for clinicians to be aware of this because these dogs are at much higher risk for developing exocrine and/or endocrine dysfunction than those with truly acute pancreatitis; in addition, they usually already have protein-calorie malnutrition at presentation, which makes their management even more challenging. It is also relatively common for dogs with chronic pancreatitis to first present with signs of DM and a concurrent acute-on-chronic bout of pancreatitis resulting in a ketoacidotic crisis. In some dogs there are no obvious clinical signs until the development of EPI, DM, or both. The development of EPI in a middle-aged to older dog of a breed not typical for pancreatic acinar atrophy has to increase the index of suspicion for underlying chronic pancreatitis. The development of EPI or DM in a dog or cat with chronic pancreatitis requires the loss of approximately 90% of exocrine or endocrine tissue function, respectively, which implies considerable tissue destruction and end-stage disease.

In cats the clinical signs of chronic pancreatitis are usually very mild and nonspecific. This is not surprising considering that cats display mild clinical signs, even in association with acute necrotizing pancreatitis. One study showed that the clinical signs of histologically confirmed chronic nonsuppurative pancreatitis in cats were indistinguishable from those of acute necrotizing pancreatitis (Ferreri et al., 2003). However, chronic pancreatitis in this species is significantly more often associated with concurrent disease than acute pancreatitis, particularly inflammatory bowel disease, cholangiohepatitis, hepatic lipidosis, and/or renal disease. The clinical signs of these concurrent diseases may predominate, further confusing diagnosis. Nevertheless, some cats will eventually develop end-stage disease with resultant EPI and/or DM.

Chronic pancreatitis is the most common cause of extrahepatic biliary obstruction in dogs (see Chapter 38), and dogs and cats with acute-on-chronic pancreatitis frequently develop jaundice.

# **Diagnosis**

# **NonInvasive Diagnosis**

In the absence of a biopsy, which is the gold standard, the clinician must rely on a combination of clinical history, ultrasonography, and clinical pathology. The findings on diagnostic imaging and clinical pathology are similar to those outlined in the section on acute pancreatitis and Tables 40-4 and 40-5. However, changes tend to be less marked in dogs and cats with chronic pancreatitis, and the diagnostic sensitivity of all tests is lower. Ultrasonography has a lower sensitivity in dogs and cats with chronic disease because

there is less edema than in those with acute disease. A variety of ultrasonographic changes may be seen in patients with chronic pancreatitis, including a normal pancreas, a mass lesion, a mixed hyperechoic and hypoechoic appearance to the pancreas, and sometimes an appearance resembling that of classical acute pancreatitis with a hypoechoic pancreas and a bright surrounding mesentery (Watson et al 2006b; see Fig. 40-6). In addition, in patients with chronic disease adhesions to the gut may be apparent, and the anatomy of the pancreatic and duodenal relationship may be changed by these adhesions. Some patients (particularly Cocker Spaniels) have large mass-like lesions associated with fibrosis and inflammation; some cases have tortuous and dilated, irregular ducts; and many cases have completely normal pancreatic ultrasonographic findings in spite of severe disease.

Likewise, clinical pathology can be helpful, but the results may also be normal. Increases in pancreatic enzyme acitivities are most likely to be seen during an acute-on-chronic bout than during a quiescent phase of disease (very similar to the waxing-and-waning increases in liver enzyme activities in patients with ongoing chronic hepatitis). Again, similar to the situation in hepatic cirrhosis, in end-stage chronic pancreatitis there may not be enough pancreatic tissue left to produce increases in enzyme activities, even in acute flare-ups. On the other hand, occasionally serum TLI can temporarily increase into or above the normal range in dogs with EPI as a result of end-stage chronic pancreatitis, confusing the diagnosis of EPI in these dogs. cPLI appears to have the highest sensitivity for the diagnosis of canine chronic pancreatitis, but even this has a lower sensitivity than in acute disease. The diagnostic sensitivity of feline PLI for chronic pancreatitis in cats is unknown.

It is important to measure serum B<sub>12</sub> concentrations in dogs and cats with chronic pancreatitis. The gradual development of EPI, combined often with concurrent ileal disease particularly in cats, predisposes to cobalamin deficiency, as outlined in the section on EPI. If serum B<sub>12</sub> concentration is low, cobalamin should be supplemented parenterally (0.02 mg/kg, administered intramuscularly or subcutaneously every 2 weeks in dogs and cats until serum concentration is normalized).

## Biopsy

The diagnosis of chronic pancreatitis can be very difficult in dogs and cats, and difficulties in diagnosis likely result in under-recognition of the disease. Establishing a definitive diagnosis relies on obtaining a pancreatic biopsy. However, this will not be indicated in most cases until there are effective treatments because a biopsy is a relatively invasive procedure, the results of which do not alter treatment or outcome. However, with the potential for some more specific therapies, routine biopsy may be indicated in the future. In humans the preferred method is needle-biopsy via transendoscopic ultrasonographic guidance. Transendoscopic ultrasonography is very expensive and of limited availability in veterinary medicine, so in dogs and cats surgical or laparo-

scopic biopsies remain the most applicable. Cytology of ultrasound-guided transcutaneous fine needle aspirates of the pancreas may help differentiate neoplasia or dysplasia from inflammation, but veterinary experience in this area is very limited. If the clinician is performing a laparotomy to obtain other biopsies, it makes perfect sense to obtain a pancreatic biopsy at that time as well. Pancreatitis is not a risk, provided the pancreas is handled gently and the blood supply is not disrupted. However, the biopsy should be small and from the tip of a lobe and may therefore miss the area of disease, which is usually patchy, particularly early on, and can also be centered on large ducts. Unfortunately therefore, even biopsy has its limitations.

# **Treatment and Prognosis**

Dogs and cats with chronic, intermittent pancreatitis may have intermittent bouts of mild gastrointestinal signs and anorexia, and the owner's primary concern is often that the pet has missed a meal. These animals can be managed at home, as long as anorexia is not long lasting, and the owner should be reassured that a short period of self-induced starvation is actually beneficial because it provides pancreatic rest.

As in patients with acute pancreatitis, the current preference is for symptomatic treatment. Dogs and cats with acute flare-ups require the same intensive treatment as dogs and cats with classical acute pancreatitis and have the same risk of mortality (see preceding section). The difference from isolated acute pancreatitis is that if the animal recovers from the acute bout, it is likely to remain with considerable exocrine and/or endocrine functional impairment. In the milder cases symptomatic treatment can make a real difference in the animal's quality of life. Changing to a low-fat diet (such as Hill's ID, Royal-Canin-Waltham Digestive low fat, or Eukanuba Intestinal) apparently reduces postprandial pain and acute flare-ups in many cases. Owners often underestimate the effects of fatty treats, which can precipitate recurrences in susceptible individuals. Some animals need analgesia, either intermittently or continuously (see section on acute pancreatitis and Table 40-8). According to anecdotal reports, short courses of metronidazole (10 mg/kg, PO q12h) seem to help some patients after acute boutspresumably because they develop secondary bacterial overgrowth as a result of a "stagnant loop" phenomenon in the adjacent duodenum. Serum B<sub>12</sub> concentration should be measured regularly, and cobalamin should be supplemented parenterally as necessary (0.02 mg/kg, administered intramuscularly 2 to 4 weeks until serum concentration normalizes).

Treatment of extrahepatic biliary tract obstruction associated with acute-on-chronic disease should be as outlined in the acute pancreatitis section.

In patients with end-stage disease, exocrine and/or endocrine deficiency may develop. Dogs and cats with EPI and/or DM are managed with enzymes (discussed in more detail later) and insulin as necessary in the usual way (see Chapter 52), and most do surprisingly well long term.

#### **EXOCRINE PANCREATIC INSUFFICIENCY**

EPI is a functional diagnosis that results from a lack of pancreatic enzymes. As such, unlike pancreatitis, it is diagnosed on the basis of clinical signs and pancreatic function tests and not primarily the results of pancreatic histopathology, although finding a marked reduction in pancreatic acinar mass on histology is supportive of a diagnosis of EPI. The pancreas is the only significant source of lipase, so fat maldigestion with fatty feces (steatorrhea) and weight loss are the predominant signs of EPI.

# **Pathogenesis**

Pancreatic acinar atrophy (PAA) is believed to be the predominant cause of EPI in dogs, but recent work has shown that end-stage chronic pancreatitis is also important in this species (Fig. 40-9; Watson and Herrtage, 2006a; Batchelor et al., 2007a). PAA has not been recognized in cats; end-stage pancreatitis is the most common cause of feline EPI (Fig. 40-10). The development of clinical EPI requires approximately a 90% reduction in lipase production and thus extensive loss of pancreatic acini. It is therefore extremely unlikely to occur after a severe bout of pancreatitis; it tends to result from chronic, ongoing disease. However, the chronic disease may be largely subclinical or only present as occasional clinical acute-on-chronic episodes, so the degree of underlying pancreatic damage may be underestimated.

PAA is particularly recognized in young German Shepherd Dogs (see Fig. 40-9, A), in which an autosomal mode of inheritance has been demonstrated, and has also been described in Rough Collies, suspected in English Setters, and sporadically reported in other breeds. A recent large study of EPI in the U.K. reported that young Chow Chows were overrepresented (Batchelor et al., 2007a). The pathogenesis was unknown, but the juvenile onset suggested PAA or perhaps a congenital defect in this breed.

Histological studies in German Shepherd Dogs suggest that PAA is an autoimmune disease directed against the acini (Wiberg et al., 2000). Therefore the islets are spared, and dogs with PAA are not typically diabetic. However, affected dogs do not respond to immunosuppressive therapy. Most dogs develop the disease in young adulthood, but a proportion of German Shepherd Dogs remain subclinical for a prolonged period of time and present only late in life.

In contrast, many dogs with end-stage chronic pancreatitis also develop DM either before or after EPI as a result of concurrent islet cell destruction (Watson, 2003; Watson et al., 2006a). The situation is similar in cats with end-stage chronic pancreatitis. There is no breed relationship in cats, but dogs with EPI as a result of end-stage chronic pancreatitis tend to be middle-aged to older medium- or small-breed dogs, particularly Cavalier King Charles Spaniels, English Cocker Spaniels, and Collies (see Fig. 40-8). Interestingly, although Boxers in the U.K. were reported to have an increased prevalence of chronic pancreatitis in one study, they have also been reported to be significantly under-



#### FIG 40-9

**A,** Physical appearance of a 2-year-old male German Shepherd Dog with exocrine pancreatic insufficiency (EPI). **B,** An 11-year-old neutered female English Springer Spaniel with EPI caused by end-stage chronic pancreatitis. This dog also had diabetes mellitus (DM) but was still losing weight in spite of good control of the DM. EPI had not initially been suspected, but once it was diagnosed and treated with enzyme supplements, the dog returned to normal weight and coat condition within 6 months (**C**). (A, Courtesy Dr. William E. Hornbuckle, Cornell University, College of Veterinary Medicine. **B,** From Journal of Small Animal Practice vol. 44, 2003.)



**FIG 40-10**A middle-aged Persian cat with end-stage chronic pancreatitis and exocrine pancreatic insufficiency. Note matting of coat with feces and poor body condition.

represented among dogs with EPI, which suggests that their chronic pancreatitis does not progress to end-stage disease. Other underrepresented breeds in a large study of EPI were Golden Retrievers, Labrador Retrievers, Rottweilers and Weimaraners (Batchelor et al., 2007a). Finding compatible clinical signs in these breeds should first trigger a search for other possible causes, such as chronic infections or inflammatory bowel disease.

Other causes of EPI in dogs and cats are pancreatic tumors, hyperacidity of the duodenum inactivating lipase, and isolated enzyme (particularly lipase) deficiency. These are all rare causes. Patients with pancreatic tumors usually present for other reasons, but tumors can result in EPI owing to a combination of compression of pancreatic ducts by the mass, destruction of acinar tissue, and associated pancreatitis.

Up to 70% of dogs with EPI have concurrent small intestinal bacterial overgrowth (SIBO). This will contribute to clinical signs and should be considered when treating an

affected dog. In SIBO bacteria deconjugate bile salts, thus decreasing fat emulsification and therefore fat digestion. Bacteria also break down the undigested fat to hydroxy fatty acids. These and deconjugated bile salts irritate the colonic mucosa and may cause large intestinal diarrhea by stimulating secretion. Dogs with EPI therefore tend to present with signs of both small and large bowel diarrhea.

A high proportion of dogs (particularly those presenting with low body condition scores) also have reduced duodenal enzyme activity, which may be partly due to the SIBO but also to the effects of malnutrition on the gut and possibly to the loss of the trophic influence of pancreatic secretions. Cobalamin deficiency is common in both dogs and cats with EPI and seems to be a negative prognostic indicator in dogs if untreated (Batchelor et al 2007b). Vitamin B<sub>12</sub> is absorbed from the distal ileum using a carrier-mediated process that requires the vitamin to be bound to intrinsic factor (IF). The latter is produced entirely by the pancreas in cats and mainly by the pancreas in dogs, although the canine stomach can also produce a small amount. Therefore most cats with EPI are expected to be B<sub>12</sub>-deficient, whereas most but not all of dogs with EPI have hypocobalaminemia. In one large study of dogs with EPI, 82% of dogs had low serum cobalamin concentration (Batchelor et al 2007b). In cats with end-stage pancreatitis, the hypocobalaminemia is compounded by the high prevalence of concurrent inflammatory bowel disease, which often decreases ileal absorption of vitamin B<sub>12</sub>. Cobalamin deficiency causes villous atrophy and reduced gastrointestinal function, weight loss, and diarrhea in cats; therefore it is important not only to document hypocobalaminemia but also to treat it with parenteral  $B_{12}$  injections (0.02 mg/kg, administered intramuscularly 2 to 4 weeks until serum concentration normalizes).

#### **Clinical Features**

Most dogs and cats with EPI present because of chronic diarrhea and emaciation in tandem with a ravenous appetite (see Fig. 40-9). The diarrhea tends to be fatty (steatorrhea) because of prominent fat maldigestion but is variable from day to day and among individuals. Sometimes diarrhea is not a prominent feature because digestion is interrupted so early in the process that the osmotic effect of molecules is relatively small. Affected dogs and cats also often have chronic seborrheic skin disease resulting from deficiency of essential fatty acids and cachexia, and some patients present to a dermatology clinic for this reason. If EPI is due to chronic pancreatitis, the diagnosis may be complicated by concurrent ongoing pancreatitis that may cause intermittent anorexia and vomiting. Animals with end-stage chronic pancreatitis may also develop DM either before or months to years after the development of EPI.

Concurrent diseases are common in dogs with EPI, either related or unrelated to the pancreatic deficiency. In one study in dogs concurrent gastrointestinal, skeletal, and skin conditions were common (Batchelor et al 2007b). Cats with pancreatitis often have concurrent cholangitis and/or inflammatory bowel disease, and it is often difficult to differentiate

the clinical signs of the three conditions because they are so similar.

# Diagnosis

## **ROUTINE CLINICAL PATHOLOGY**

CBCs and serum biochemistry profiles are often normal in dogs and cats with EPI. In very cachectic animals there may be subtle nonspecific changes consistent with malnutrition, negative nitrogen balance, and breakdown of body muscle such as low albumin and globulin concentrations, mildly increased liver enzyme activities, low cholesterol and triglyceride concentrations, and lymphopenia.

Finding marked hypoproteinemia or more severe changes on the CBC and biochemistry profiles in an animal with EPI should trigger a search for another concurrent disease. Cats and dogs with end-stage pancreatitis may present with more severe secondary clinicopathologic changes, as outlined in the pancreatitis section. A high percentage of these patients with end-stage pancreatitis (up to 50%) also have concurrent DM, so they have clinicopathological changes typical of DM (see Chapter 52).

#### **PANCREATIC ENZYMES**

The diagnosis of EPI in dogs and cats relies on demonstrating reduced pancreatic enzyme output. The most sensitive and specific way of doing this is by measuring reduced circulating enzyme activity. Blood tests that indirectly measure gut enzyme activity, such as the BT-PABA test, are now rarely used because they have been replaced by the specific immunoassays for serum activities of pancreatic enzymes. Readers who would like more information on the BT-PABA test are referred to Batt et al. (1981). The plasma turbidity test, used historically after feeding a high-fat meal, with and without pancreatic enzymes, had a very low sensitivity and specificity for EPI and has been completely superseded by the enzymatic test.

Measurement of reduced TLI in the blood has a high sensitivity and specificity for the diagnosis of EPI in dogs and cats and is currently the single test of choice for the diagnosis of EPI in small animals. It is important to measure it on a fasting sample because the release of pancreatic enzymes associated with feeding can raise the levels in the serum. It is not necessary to stop exogenous pancreatic enzyme supplementation before measuring TLI because exogenous enzymes should not be absorbed from the gut into the circulation; even if they are, the test is an immunoassay that does not cross-react with the tryspin/trypsinogen of other species in the supplement. However, there are some problems in interpreting the results, as listed in Box 40-2.

Unlike in humans, amylase and lipase activities are not consistently low in dogs and cats with EPI because of the high background levels of enzymes from other organs. A low cPLI also has a good sensitivity and specificity for the diagnosis of EPI in dogs (Steiner et al., 2001). However, this test is not superior to TLI. PLI is also likely to be low in cats with EPI.



BOX 40-2

# Interpretation of TLI Results in the Diagnosis of Canine Exocrine Pancreatic Insufficiency

- A low serum TU (<2.5 µg/l in dogs) in a dog with compatible clinical signs, particularly in a high-risk breed, is diagnostic of EPl</li>
  - A repeat blood sample to confirm diagnosis in a few weeks to months is recommended in cats and in older dogs that are not German Shepherd Dogs. Occasionally, a single TLI may be low in a dog with pancreatitis as a result of a temporary reduction in enzyme production.
- A low serum TU (<2.5 µg/l in dogs) with no compatible clinical signs (i.e., no weight loss or diarrhea) is not diagnostic of EPI but should be repeated
  - A dog with persistently low TLI but no steatorrhea or weight loss should be considered to have subclinical EPI and should not be treated but monitored for any evidence of clinical disease. A TLI stimulation test may give more information about the status of the animal but is rarely performed. Subclinical EPI has been reported in a small number of German Shepherd Dogs with PAA (Wiberg et al 1999) but has not yet been reported in cats. It is uncommon.
- A TLI in the gray area (2.5-5.0 μg/l in dogs) is not diagnostic of EPI and should be repeated in a few weeks to months.
  - In a proportion of dogs (45% in one study: Wiberg et al., 1999), the TLI will return to the normal range.

- In another proportion of dogs (about 10%), the TLI will decrease to the level diagnostic of EPI and in some it may remain in the grey area.
- In an older dog that is not a German Shepherd Dog, TLI values may fluctuate as described below and samples should be repeated when there is no clinically acute flare-up
- A normal TLI in a German Shepherd Dog rules out EPI resulting from PAA, and a search should be made for another cause of the presenting clinical signs.
- A single normal or high TLI in an older nonGerman Shepherd Dog with suspicious clinical signs does not rule out EPI. TLI can transiently and intermittently increase into or above the normal range in dogs with EPI secondary to chronic end-stage pancreatitis if it is measured during a bout of inflammation. This is understandable because EPI reduces TLI but pancreatitis elevates it, so the two conditions occurring concurrently interfere with interpretation of the test. This is likely to be true in cats as well, although it has not been well documented in that species. Therefore in any animal with suspected EPI secondary to chronic pancreatitis, TLI measurements should be repeated, preferably when the animal is showing no clinical signs of pancreatitis. Alternatively, a test for enzyme activity in the gut such as a fecal elastase test could be used in these animals.

Note: A TLI stimulation test could be used in animals with subclinical EPI (low TLI but no clinical signs) or animals with a TLI persistently in the grey area. Pancreatic enzyme output is stimulated either with intravenous cholecystokinin and secretin or with a test meal, and TLI concentrations are measured before and after stimulation (Wiberg et al., 1999). Animals with true clinical EPI show no stimulation, whereas animals with subclinical EPI still have enough enzyme activity to increase their TLI after stimulation. The value of a stimulation test in clinical cases is limited because the decision to treat is based on the clinical signs. It is of more value in monitoring progression of disease for clinical research.

EPI, Exocrine pancreatic insufficiency; PAA, pancreatic acinar atrophy.

Fecal tests for EPI are rarely used because of low sensitivity and specificity compared with serum tests. Measuring fecal trypsin activity has a very low sensitivity and specificity for EPI, as do assessment of fecal proteolytic activity or microscopic examination of feces for undigested fat, starch, and muscle fibers. All these tests have been superseded by measurement of serum TLI and cPLI. Measurement of fecal elastase may have some utility in dogs with EPI as a result of chronic pancreatitis or duct blockage, in which TLI results may be misleading. Elastase appears to have higher sensitivity and specificity than the other fecal tests for the diagnosis of EPI in dogs. Elastase is a pancreatic enzyme, and a speciesspecific ELISA for canine elastase has been developed and is available for commercial use in dogs (Spillman et al., 2000 and 2001). As with canine TLI, because there is no crossreaction with elastase from other species, dogs can remain on enzyme supplementation while the test is performed. There is marked variation in elastase levels in normal canine feces compared with humans. The sensitivity and specificity of the test are improved by taking three separate fecal samples

on three days or using a cut-off value for diagnosis of EPI, which is below this variation in most dogs.

# **OTHER DIAGNOSTIC TESTS**

It is also advisable to measure serum cobalamin concentration in animals with EPI because cobalamin concentration is often reduced because of a deficiency of pancreatic intrinsic factor, as previously explained. If serum  $B_{12}$  concentration is low, it should be supplemented parenterally. (0.02 mg/kg, administered intramuscularly every 2 to 4 weeks until serum concentration normalizes).

Serum folate concentrations are high in about a third of dogs with EPI. This may indicate SIBO, although the sensitivity and specificity of high serum folate concentration for the diagnosis of SIBO is poor. The definition and diagnosis of SIBO is problematic, and it is better to assume that a newly diagnosed dog with EPI has SIBO and treat it appropriately than to rely on the results of diagnostic tests. The importance of SIBO in cats with EPI is unknown. Occasionally in dogs and cats with EPI, serum folate concentration

may be low; this can suggest either dietary deficiency or concurrent inflammatory or infiltrative disease in the jejunum. Unlike cobalamin, there is no clear evidence that folate should be supplemented in dogs when it is low.

# Treatment **DRUGS**

All dogs and cats with clinical EPI require enzyme supplementation for life. In most cases this is provided as a powder or in the form of a capsule, which is opened and then sprinkled on the food. Fresh raw pancreas (which can be frozen in aliquots) may be used as an alternative and can be very effective, but there is also the potential for acquiring gastrointestinal infections (such as Salmonella and Campylobacter). The dose of enzymes is initially as recommended by the manufacturer and then titrated to the individual. A large proportion of enzyme activity is lost in the acid pH of the stomach (up to 83% of lipase activity and 65% of trypsin activity). To overcome this, either the dose of enzymes given is increased or an H2 blocker is administered concurrently to increase gastric pH. Preincubating enzymes with the food is not indicated because they require the alkaline environment of the small intestine to work properly. In the long term it is often possible to decrease the dose of enzymes given (but not stop altogether). This may be due to resolution of the secondary bacterial overgrowth and the effects of chronic malnutrition and cobalamin deficiency on enterocytes and brush border enzymes. Reports suggest that enzyme replacement may be reduced over the long term by between 6% and 58% but not stopped altogether.

Dogs and cats with EPI and concurrent SIBO require courses of appropriate antibiotics (oxytetracycline, tylosin, or metronidazole). It is advisable to administer prophylactic medication for presumed SIBO in all newly diagnosed cases for 3 to 4 weeks in view of the high prevalence of concurrent bacterial overgrowth and the difficulty in diagnosing it, although it remains unclear whether initial antibiotic therapy improves prognosis.

Dogs and cats with documented hypocobalaminemia will require parenteral vitamin B<sub>12</sub> injections (0.02 mg/kg, administered intrumuscularly every 2 to 4 weeks until serum concentration normalizes). It is relatively common for German Shepherd Dogs with PAA to have concurrent inflammatory bowel disease, and this must also be addressed. Animals with EPI as a result of chronic pancreatitis may require insulin therapy for concurrent DM and other therapies for acute flare-ups, including analgesics, as outlined in the section on pancreatitis.

# DIET

Disruption of fat digestion is the most important feature of EPI. A low-fat food has therefore been traditionally recommended, but it may not contain enough calories to feed a large-breed dog (e.g., a German Shepherd Dog) effectively. Fat usually contributes a significant proportion of daily energy intake because it is more energy-dense than carbohydrates. In large-breed dogs with EPI and cachexia, weight

gain may be very difficult to achieve with a low-fat diet. There is no convincing evidence in the literature that longterm feeding of a low-fat diet improves outcome in dogs with PAA, although there is some evidence that it may result in faster resolution of clinical signs. However, high-fat diets (such as proprietary renal diets) should obviously be avoided. We therefore recommend that dogs with PAA be fed a normal to moderately fat-restricted, highly digestible diet with reasonable calorie density. The diet should also be low in fiber because fiber impairs the activity of pancreatic enzymes and soluble fiber may actually absorb pancreatic enzymes. Fiber may also reduce small intestinal absorption and activity of brush border enzymes. The proprietary veterinary diets marketed for gastrointestinal disease in dogs (e.g., Hill's ID, Royal-Canin Digestive low fat HF, and Eukanuba Intestinal or Dermatosis FP) fulfill these requirements and are recommended, at least for initial stabilization. In the long term, after the gut wall recovers, these dogs can be maintained on a normal fat level in most cases and can often return to their normal diet. In some individuals with PAA extra calories can be added to the diet between meals in the form of medium chain triglycerides, such as coconut oil. They should not be used in cats and should not be given in overly high doses in dogs because of the risk of osmotic diarrhea. The recommended daily amount is 1/4 to 4 teaspoons in dogs in divided doses. Medium chain triglycerides also cannot carry fatsoluble vitamins, will cause vomiting in some individuals, and are contraindicated in dogs with liver disease because they may worsen encephalopathy.

In dogs with EPI as a result of CP, dietary advice is slightly different. Many of these dogs benefit from long-term feeding of a low-fat diet, which seems to reduce postprandial pain and acute flare-ups of disease (Hill's ID; Royal-Canin Digestive low fat, or Eukanuba Intestinal). Therefore proprietary low-fat diets would be preferred in these patients. The use of medium chain triglycerides is not recommended in dogs with chronic pancreatitis, but fortunately these are often small-breed dogs with less cachexia than the German Shepherd Dogs with PAA.

It is best to feed two or more meals a day, each with enzymes added, and the dog should not be allowed to scavenge. This is often difficult because they are polyphagic, but scavenging, especially of fatty foods, causes recurrence of diarrhea and sets back recovery.

Cats with EPI are often best managed on a hypoallergenic intestinal type diet (e.g., Hill's DD, Eukanuba dermatosis LB, or Royal-Canin limited ingredient diets) because there is a high incidence of concurrent inflammatory bowel disease. If they are also diabetic, it is unclear whether they should be fed an intestinal diet or a proprietary feline diabetes diet (e.g., Hill's MD, Royal-Canin diabetic diet, or Purina DM).

#### **Prognosis**

The prognosis for dogs with EPI is good because the disease can be treated. However, a surprising number of dogs (19% in one recent study) are euthanized within the first year of treatment because of poor response to therapy (Batchelor et al., 2007b). The same study showed that the median survival time of dogs that responded to treatment was very good, at 1919 days. This underlines the importance of scheduling regular follow-up appointments, particularly in the initial stages of therapy, to evaluate progress and change management as necessary. Prognosis for dogs and cats with EPI as a result of end-stage chronic pancreatitis is surprisingly good in most cases, even if it is complicated by concurrent DM, with survival times of several years in most cases.

# **EXOCRINE PANCREATIC NEOPLASIA**

Neoplasms of the exocrine pancreas are uncommon in both cats and dogs. Pancreatic adenocarcinomas have a very aggressive biological behavior and have usually disseminated widely by the time of diagnosis. They are often subclinical until they have disseminated, but they can result in single or repeat bouts of pancreatitis and/or the development of EPI. Some pancreatic tumors have been associated with paraneoplastic syndromes such as sterile panniculitis in dogs, alopecia with shiny skin in cats, and hypercalcemia. Chronic pancreatitis is a risk factor for the development of pancreatic adenocarcinomas in humans, and this may also be true in dogs because the published reports of these tumors in dogs show a predominance of Cocker and Cavalier King Charles spaniels.

Pancreatic adenomas are rare in small animals but have been reported in cats. Nodular hyperplasia of the exocrine pancreas is also common in older dogs and cats. This usually presents as multiple small masses, whereas pancreatic tumors are usually single, but histopathology or cytology is necessary to definitively differentiate hyperplasia from neoplasia. Both dogs and cats with acute and chronic pancreatitis sometimes present with a large pancreatic "mass" as a result of fat necrosis and/or associated fibrosis, and it is important not to confuse these with neoplasia. Again, histopathology is required to differentiate these conditions. Ultrasound-guided fine needle aspiration cytology has been suggested as a useful means of differentiating inflammatory and neoplastic lesions of the pancreas (Bjorneby and Kari, 2002). Clinical use in dogs and cats is limited, but it has been reported to be helpful in diagnosis in some studies (Bennet et al., 2001).

Pancreatic tumors are not associated with any specific clinicopathological changes and may cause no changes in enzymes at all. Alternatively, they can result in recurrent bouts of pancreatitis with typical associated blood changes, and EPI can develop. In some cases biliary tract obstruction may occur with associated jaundice and marked elevations in liver enzyme activities. Occasionally, pancreatic tumors have been reported associated with marked hyperlipasemia.

The prognosis in dogs and cats with pancreatic adenocarcinoma is very poor. The tumors are extremely aggressive, poorly sensitive to chemotherapy or radiotherapy, and have usually disseminated widely by the time of diagnosis. Neuroendocrine tumors such as insulinomas and gastrinomas appear to be more common than pancreatic adenocarcinomas in dogs and tend to be seen in different breeds of dog, predominantly large breeds (Watson et al., 2007). These are tumors of the endocrine pancreas that produce clinical signs related to secretion of hormones and are therefore outside the scope of this chapter.

# PANCREATIC ABSCESSES, CYSTS, AND PSEUDOCYSTS

Pancreatic abscesses, cysts, and pseudocysts are uncommonly reported in dogs and cats and are usually a complication or sequela of pancreatitis. Pancreatic cysts may be congenital (e.g., as part of the polycystic renal disease in Persian cats) or secondary to cystic neoplasia, but the most common are pseudocysts secondary to pancreatitis. A pancreatic pseudocyst is a collection of fluid containing pancreatic enzymes and debris in a nonepithelialized sac. Pseudocysts have been recognized in association with pancreatitis in both cats and dogs, although they appear to be rare, and microscopic acinar cysts were found frequently in feline chronic pancreatitis. Pseudocysts are not associated with any distinct clinicopathological findings other than those associated with the underlying pancreatitis. Analysis of fluid obtained from a pseudocyst by fine needle aspiration generally shows a modified transudate. The activities of amylase and lipase can be measured in the pseudocyst fluid. In humans the enzymes are higher in pseudocysts associated with pancreatitis than in those associated with cystic carcinomas, but the value of this measurement in small animals is unknown. Cytology can differentiate a pseudocyst from a true abscess because a pseudocyst contains amorphous debris; some neutrophils and macrophages; and, rarely, small numbers of reactive fibroblasts, whereas an abscess contains many degenerative neutrophils and variable numbers of pancreatic acinar cells, which may appear very atypical as a result of inflammation.

A true pancreatic abscess is a collection of septic exudate that results from secondary infection of necrotic pancreatic tissue or a pancreatic pseudocyst. They are associated with a poor prognosis but fortunately are rare in dogs and cats.

Treatment of pancreatic pseudocysts can be surgical or medical. Medical treatment by ultrasound-guided cyst aspiration has had a reasonable success rate. Pancreatic abscesses should be treated surgically with omentalization or open peritoneal drainage. Both carry a high mortality rate, but a recent study suggested that omentalization may be preferable (Johnson et al., 2006).

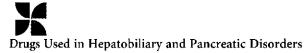
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DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
ANALGESICS ANTIBACTERIALS		See Table 40-8
Amoxicillin and ampicillin	10-20 mg/kg PO, SC, or IV q8-12h dogs and cats	Broad-spectrum bactericidal and therapeutic levels in liver and bile Biliary tract infections; control of gut bacteria in hepatic encephalopathy; control of systemic infection of gut origin
Cephalexin	10-20 mg/kg PO, SC, or IV q8-12h dogs and cats	Preferably used on basis of culture and sensitivity Very similar activity and spectrum to ampicillin—see ampicillin Helpful in patients with penicillin hypersensitivity; <10% show cross-reaction to cephalexin
Enrofloxacin (Baytril)	5 mg/kg SC or PO q24h dogs and cats	Bactericidal particularly against gram negatives; poor efficacy against anaerobes and strep; good tissue penetration Bilary tract infections, particularly with gram-negative organisms Also infectious complications of pancreatitis Preferably used on basis of culture and sensitivity; should not be used in growing dogs (toxic to growing cartilage); used only with care in cats: risk
Marbofloxacin (Zeniquin)	2 mg/kg SC, PO, or IV q24h dogs and cats	of retinal damage As enrofloxacin
Metronidazole	10 mg/kg PO or slowly IV q12h dogs and cats  If significant hepatic functional impairment, reduce to 7.5 mg/kg q12h	Bactericidal particularly effective against anaerobes; often used in combination with ampicillin for biliary tract infections or to control gut bacteria in hepatic encephalopathy
Neomycin	20 mg/kg q6-8h PO or as a retention enema dogs and cats	Particularly used in acute hepatic encephalopathy; systemic absorption and oto- and nephrotoxicity can occur if there is concurrent GI ulceration, particularly in cats.
Potentiated sulphonamides, (e.g., trimethoprim-sulpha)	15 mg/kg of combined ingredients (trimethoprim + sulphonamide) PO q12h	Bactericidal, broad-spectrum and probably drug of choice with infectious complications of pancreatitis; should not be used in liver disease if possible because hepatotoxic in susceptible individuals; should not be used in Doberman Pinschers because of reduced hepatic clearance; immune-mediated diseases occasional adverse effects
ANTIEMETICS Chlorpromazine	0.2-0.4 mg/kg SC q8h dogs and cats	Indicated in vomiting associated with pancreatitis and some cases of hepatitis, but only if other antiemetics tried and ineffective because it is a phenothiazine sedative; effective antiemetic but also sedative, so ensure adequate hydration and avoid or use very low dose in encephalopathy and cardiovascular compromise
Metoclapramide	0.2-0.5 mg/kg PO or SC q8h or 1 mg/kg q24h as a constant rate infusion	Indicated in vomiting associated with liver disease and some cases of pancreatitis; however, peripheral prokinetic effect may increase pain in pancreatitis; neurological adverse effects occasionally seen; avoid in encephalopathy



DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Maropitant (Cerenia)	Dogs only: 1 mg/kg SC q24h for up to 5 days or 2 mg/kg orally q24h for up to 5 days	Centrally acting antiemetic in new class [NK <sub>1</sub> receptor antagonist]; antiemetic of choice in canine pancreatitis as no obvious prokinetic effect; used with care in liver disease because metabolized in the liver, so do not use if significant liver dysfunction; not licensed for cats
Ondansetron (Zofran)	Cats and dogs: 0.5 mg/kg IV loading dose followed by 0.5 mg/kg/hour infusion q6h or 0.5-1 mg/kg PO q12-24h	Refractory vomiting; may be contraindicated in pancreafitis because it has been reported to trigger it in humans
ANTIENCEPHALOPATHIC	φ	
Lactulose	5-15 ml PO q8h (dogs) 0.25-1 ml PO q8h (cats) Can also be given as retention enema in acute encephalopathy See antibacterial section	Hepatic encephalopathy with acquired or congenital portosystemic shunts; overdose produces diarrhea; titrate to effect (= 2-3 soft bowel movements a day)
Antibiotics (e.g., ampicillin, metronidazole, neomycin)	See antibacterial section	
Propofol	Constant rate infusion; rate calculated by giving an initial bolus to effect (usually about 1 mg/kg) and timing duration of action; usually about 0.1-0.2 mg/kg/min	Drug of choice for seizures because of liver disease/ hepatic encephalopathy; should not be used in pancreatitis because it is a lipid vehicle
Phenobarbital	5-10 mg/kg PO q24h preoperatively followed by 3- 5 mg/kg q12h postoperatively for 3 weeks	Can be used prophylactically before and immediately after surgery to reduce risk of postoperative seizures after ligation of PSS, but evidence of effectiveness is anecdotal
ANTIINFLAMMATORY and ANTIFIBROTIC		• · · · · · · · · · · · · · · · · · · ·
Prednisolone (prednisone)	Antiinflammatory dose: 0.5 mg/kg q24h; immunosuppressive dose: 1-2 mg/kg q24h. Taper at 0.5 mg/kg q24h or eod	Antiinflammatory or immunosuppressive doses in lymphocytic cholangitis in cats and chronic hepatitis in dogs and in suspected immune-mediated pancreatitis in English Cocker spaniels  Avoid in suppurative cholangitis; avoid in portal hypertension or animals with ascites (potential GI ulceration); avoid use of dexamethasone because very ulcerogenic
Colchicine	Dogs only 0.03 mg/kg/day PO	Antifibrotic of choice in moderate hepatic fibrosis in dogs, but efficacy unclear; monitor blood samples for bone marrow suppression; GI side effects common and most likely reason to stop therapy
ANTIOXIDANTS		common and most many rousem to stop marapy
S-adenosylmethionine	Dogs: 20 mg/kg PO q24h or	Indicated in any liver disease but particularly hepatic
(SAM-e) (Denosyl)	higher; cats: 20 mg/kg or 200-400 mg total daily	lipidosis in cats and toxic hepatitis and diseases causing biliary stasis in dogs and cats; tablets must be given whole on an empty stomach for effective absorption
Sylmarin (silymarin, silibin)	50-200 mg/dog PO q24h	Antioxidant derived from milk thistle; likely effective and safe, but very limited studies to base dose advice on in dogs; studies were in toxic hepatitis
Vitamin E (tocopherol)	400 IU per day for medium-sized dogs (titrate accordingly for other sizes) or 5-25 IU/kg PO daily dogs and cats	Indications as SAMe but including any chronic hepatitis in dogs



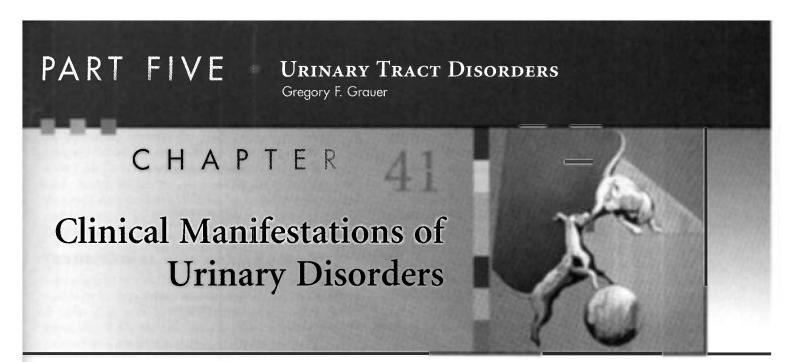
Drugs Used in Hepatobiliary and Pancreatic Disorders—cont'd

DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
Zinc (see copper chelating) and ursodeoxycholic acid (see choleretic) also have antioxidant activities ANTIDOTES		
N-acetylcysteine	Cats and dogs: 140 mg/kg IV or PO as a loading dose and then continued at 70 mg/kg q6h for a total of 7 treatments or for up to 5 days	Antidote for acetaminophen toxicity that binds the toxic metabolite and increases the glucuronidation process; can cause nausea and vomiting when given orally; foul taste makes oral dosing difficult without nasogastric tube
Cimetidine	Dogs: 5-10 mg/kg IV, IM, or PO q6-8h; Cats 2.5-5 mg/kg IV, IM, or PO q8-12h	Slows oxidative hepatic drug metabolism by binding to microsomal cytochrome P450; therefore useful additional antidote in acetaminophen toxicity in dogs and cats
Also antioxidants such as S-adenosylmethionine and vitamins E and C supportive for oxidant toxins such as acetaminophen ANTIULCER TREATMENT	See sections on antioxidants and vitamins	·
Ranitidine (Zantac)	2 mg/kg PO or slowly IV q12h dogs and cats	Acid secretory inhibitor of choice in liver disease; may not be necessary if gastric pH is high; Cimetidine should be avoided because of action on P450 enzymes, except as an antidote (see above)
Sucralfate (Carafate) COPPER CHELATING	Dogs: 1 g per 30 kg 4 times a day. Cats: 250 mg/cat PO q8-12h	Gastric ulceration associated with liver or pancreatic disease
Penicillamine	Dogs only: 10-15 mg/kg PO q12h	Copper chelator for copper storage disease; takes months to de-copper liver; give on an empty stomach; vomiting common; Immune-mediated, renal, and skin disease possible
2,3,2-tetramine tetrahydrochloride (2,3,2– T) and 2,2,2-tetramine tetrahydrochloride	Dogs only: 10-15 mg/kg PO q12h	Copper chelator for copper storage disease in dogs; more rapid effect than penicillamine so may be more useful in acute disease; 2,3,2-tetramine produces greater copper loss but is not available as a drug; isolated case reports of their use in dogs but no extensive trials; toxicity data unclear except that prolonged use may lead to clinical signs resulting from low copper levels
Zinc acetate or sulphate	1-20 mg/kg/day of elemental zinc dogs; 7 mg/cat/day of elemental zinc cats	Indicated in copper storage disease to reduce copper absorption; also antioxidant, antifibrotic, and increases ammonia detoxification, so may be helpful in any chronic hepatitis or hepatic encephalopathy; monitor blood levels every 1-2 weeks and keep below 200-300 µg/dl to avoid toxicity (iron deficiency and hemolysis); main side effect is vomiting—give 1 hour before food to minimize this
CHOLERETIC Ursodeoxycholic acid (Ursodiol)	4-15 mg/kg per day split into two doses 12 hours apart (dogs); 15 mg/kg PO once a day (cats)	Choleretic + also moderates bile acid pool to be less toxic + antiinflammatory and antioxidant; indicated in conditions associated with biliary stasis but without complete bile duct obstruction; contraindicated with obstruction in case of gallbladder rupture



DRUG NAME (TRADE NAME)	DOSAGE	INDICATIONS AND COMMENTS
DIURETIC		
Furosemide	2 mg/kg PO q8-12h dogs and cats	Use as additional divretic where necessary in ascites of liver disease; always use concurrent spironolactone to avoid compensatory increase aldosterone action with further water retention and hypokalaemia
Spironolactone	2-4 mg/kg day in divided doses dogs and cats	Diuretic of choice in ascites of liver disease (see text Chapter 39); Gradual onset of action over 2-3 days; may be combined with furosemide for more marked diuresis
TREATMENT OF COAGULOPATHIES		
Fresh frozen plasma	Dogs and cats: starting dose of 10 ml/kg; the dose of plasma is titrated based on the results of the OSPT and APTT	Replenish depleted clotting factors in severe acute or chronic liver disease, particularly if prolonged OSPT and/or APTT and no response to vitamin K treatment alone
Vitamin K1 (Phytomenadione) (Konakion)	0.5-2 mg/kg SC or IM 12 hours before biopsy and then q12h for 3 days	Treatment of coagulopathy associated with liver disease, particularly if concurrent biliary stasis and/ or gut disease reducing vitamin K absorption; treatment of coagulopathy before liver biopsy
VITAMINS		στο
Vitamin B <sub>12</sub> (Cyanocobalamin)	Dogs and cats: 0.02 mg/kg IM or SC every 2-4 weeks until serum concentration normalizes (oral dosing ineffective in EPI because of ineffective absorption)	Treatment of vitamin B <sub>12</sub> deficiency, particularly associated with EPI and lack of pancreatic intrinsic factor
Vitamin K1(Phytomenadione)	See treatment of coagulopathy section	
Vitamin E	See antioxidant section	
Vitamin C (ascorbic acid)	Cats and dogs oxidant toxins: 30-40 mg/kg SC q6h for 7 treatments	Indicated only as supportive treatment for oxidant toxins affecting the liver (e.g., acetaminophen)  Not indicated in other cases of hepatitis or copper storage disease because increases absorption and hepatic build-up of metals

PO, By mouth; SC, subcutaneous; IV, intravenous; GI, gastrointestinal; PSS, portosystemic shunt; IM, intramuscular; EPI, exocrine pancreatic insufficiency.



# CHAPTER OUTLINE

#### GENERAL CONSIDERATIONS

Pollakiuria and Dysuria-Stranguria Urethral Obstruction Urinary Tract Infection Transitional Cell Carcinoma Urolithiasis Feline Lower Urinary Tract Inflammation Hematuria

DISORDERS OF MICTURITION
Initial Evaluation
Pharmacologic Testing and Treatment
Distended Bladder
Small or Normal-Sized Bladder
POLYDIPSIA AND POLYURIA
PROTEINURIA
AZOTEMIA
RENOMEGALY

# **GENERAL CONSIDERATIONS**

This chapter begins with a discussion of urinary tract problems that are likely to be identified by pet owners (e.g., pollakiuria and dysuria-stranguria, hematuria, urinary incontinence, and polydipsia and polyuria). Problems that are usually identified on the basis of a physical examination, a minimum database, or with imaging techniques, including proteinuria, azotemia, and renomegaly, are discussed subsequently.

# POLLAKIURIA AND DYSURIA-STRANGURIA

Lower urinary tract inflammation (LUTI) usually results in increased frequency of urination (pollakiuria) and difficult urination (dysuria) associated with straining (stranguria; Fig. 41-1). LUTI in dogs is often caused by bacterial infection; in contrast, primary bacterial infection of the urinary tract is relatively rare in cats. Sterile inflammation (e.g., some cases of calcium oxalate urolithiasis and idiopathic cystitis) or space-occupying masses of the lower urinary tract (e.g., neoplasia, ureterocele) can result in pollakiuria and dysuriastranguria in both dogs and cats. When an animal has clinical signs suggestive of LUTI or obstruction, transabdominal palpation of the bladder may confirm the presence of a distended bladder, a thickened bladder wall, a bladder mass, or urolithiasis. If possible, urinary bladder palpation should be performed before and after the patient voids because a full bladder may obscure the presence of intraluminal masses or uroliths. Digital rectal examination in smaller male and female dogs and in cats often allows the clinician to evaluate the trigone of the bladder and the pelvic urethra in a search for masses or uroliths. Urinalysis, urine bacterial culture, ultrasonography of the bladder, and/or plain or contrastenhanced radiography of the bladder and urethra often demonstrate the cause of the pollakiuria and dysuriastranguria; occasionally, advanced imaging modalities (e.g., computed tomography (CT) scan) may be necessary to evaluate the lower urinary tract. Currently, cystoscopy is widely used in specialty practices and academic hospitals for evaluation of patients with lower urinary tract diseases. If systemic signs (e.g., depression, lethargy, anorexia, vomiting) are present in animals with LUTI, a complete blood count (CBC) and serum biochemistry profile should also be obtained, and the kidneys, prostate, and uterus/uterine stump should be evaluated as a possible source of the signs.

# **URETHRAL OBSTRUCTION**

Urethral obstruction, either functional (e.g., reflex dyssynergia, urethral spasm) or anatomic (e.g., urolithiasis, granulomatous urethritis, neoplasia), usually causes pollakiuria, dysuria-stranguria, or both, with an attenuated or absent urine stream. A urethral catheter will pass relatively easily in

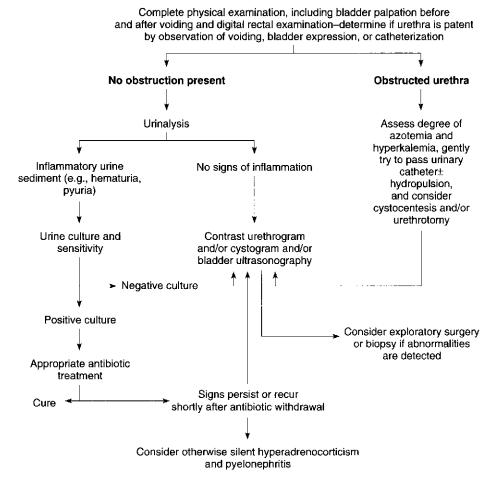


FIG 41-1 Diagnostic approach to pollakiuria and dysuria-stranguria (see also Fig. 41-7).

TABLE 41-1

Numbers of Bacteria per Milliliter Considered Significant According to Method of Urine Collection in Dogs and Cats

COLLECTION METHOD	SIGNIFICANT	QUESTIONABLE	CONTAMINATION
Cystocentesis	>1000	100 to 1000	<100
Catheterization	>10,000	1000 to 10,000	<1000
Voided or expressed	>100,000	10,000 to 100,000	<10,000

patients with a functional obstruction, whereas an anatomic obstruction will result in "grating," difficult passage or the inability to pass the catheter. If there is any question, a positive contrast retrograde urethrogram will confirm the presence of an anatomic lesion or obstruction. If a complete urethral obstruction exists, the degree of postrenal azotemia and hyperkalemia should be assessed immediately. Hyperkalemia can cause life-threatening cardiac arrhythmias and should be treated promptly (see Fig. 41-1).

#### URINARY TRACT INFECTION

Urine for urinalysis and bacterial culture may be obtained by antepubic cystocentesis, urinary bladder catheterization, or a midstream catch during voiding. However, the number of organisms isolated in a normal dog or cat varies according to the technique used (Table 41-1). Ideally, urine should be obtained by cystocentesis, and urine specimens should be plated within 30 minutes of collection. If this is not possible, the urine sample should be refrigerated in a closed container because bacteria may double their numbers in urine every 45 minutes at room temperature, resulting in false-positive culture findings. On the other hand, false-negative urine culture results may be obtained if the urine has been frozen or refrigerated for 12 to 24 hours or more.

Animals with recurrent or refractory urinary tract infections (UTIs) should undergo ultrasonography or contrast-

enhanced radiography in a search for underlying anatomic disorders. Bladder tumors or polyps, uroliths, pyelonephritis, prostatitis, ureteroceles, and urachal remnants are common causes of recurrent or unresponsive UTIs. In some cases, systemic disorders such as hyperadrenocorticism, chronic kidney disease, and diabetes mellitus may be associated with recurrent UTIs, as can long-term corticosteroid treatment. UTIs are discussed in greater depth in Chapter 45.

#### TRANSITIONAL CELL CARCINOMA

Transitional cell carcinoma (TCC) is the most common malignant bladder tumor in dogs and should be suspected in older dogs with hematuria, pollakiuria, and dysuriastranguria. TCCs are rare in cats, where they are usually detected as a diffuse thickening of the bladder wall during palpation or imaging. TCCs most frequently arise in the bladder trigone region; therefore rectal palpation can often detect their presence. Urinary bladder ultrasonography or double contrast-enhanced cystography will confirm that a bladder mass exists. In some cases, unilateral or bilateral hydroureter-hydronephrosis is observed as a result of obstruction of one or both ureters at the vesicoureteral junction. Tumor biopsy and histopathologic evaluation should be done to confirm the tumor type and stage and to direct the nature of specific treatment. The bladder tumor antigen test (V-BTA test: www.polymedco.com) is usually not recommended as a diagnostic aid because it does not reliably differentiate dogs with bladder cancer from dogs with LUTI resulting from other causes. In some specialty practices, cystoscopy provides a simple method to obtain a diagnostic sample for histopathology and assess the extent of bladder involvement in dogs and cats with infiltrative bladder diseases.

# **UROLITHIASIS**

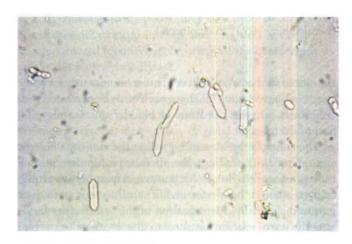
Urinary bladder and urethral uroliths can often be palpated during abdominal or rectal examination; however, a full bladder or a thickened, inflamed bladder wall may obscure small uroliths. In male dogs with dysuria, the urethra should be palpated subcutaneously from the ischial arch to the os penis in a search for urethral uroliths. Ultrasonography or plain or contrast-enhanced radiography of the urinary tract may be necessary to confirm the presence of uroliths. Calcium oxalate and struvite uroliths are the most radiodense, whereas urate uroliths are relatively radiolucent, and contrast-enhanced radiographs may be required for their diagnosis. Silicate and cystine uroliths have an intermediate radiodensity, and unless the stones are small (<5 mm in diameter), they can usually be observed on plain film radiographs.

Urinalysis findings in dogs and cats with urolithiasis often indicate the presence of urinary tract inflammation (e.g., hematuria, pyuria, increased numbers of epithelial cells, and proteinuria). The urine pH varies depending on the stone type, on the presence or absence of a concurrent bacterial infection, and on the animal's diet. In general, struvite uroliths are associated with an alkaline urine (especially if

urease-producing bacteria are present); cystine uroliths with an acidic urine; and oxalate, urate, and silicate uroliths with a neutral-to-acidic urine. Crystalluria may be observed depending on the urine concentration, pH, and temperature. Although crystalluria may exist in the absence of uroliths, and uroliths may be present in the absence of crystalluria, if the two coexist, the identity of the crystals is usually the same as that of the urolith (Figs. 41-2 to 41-6). Exceptions do occur, however; for example, a urease-producing bacterial infection could generate struvite crystals in the presence of silicate or calcium oxalate uroliths. Bacterial urine culture and sensitivity testing should be performed in all animals with urolithiasis to identify and properly treat any concurrent UTI. If a cystotomy is performed to remove stones, a small piece of the bladder mucosa or urolith should be



FIG 41-2
Struvite crystals in urine sediment. These crystals are normally colorless. (From Grauer GF: Canine urolithiasis. In Allen DG, editor: *Small animal medicine*, Philadelphia, 1991, JB Lippincott.)



Monohydrate calcium oxalate crystals in urine sediment. These crystals are normally colorless. (From Grauer GF: Canine urolithiasis. In Allen DG, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)

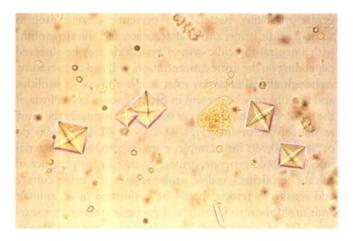


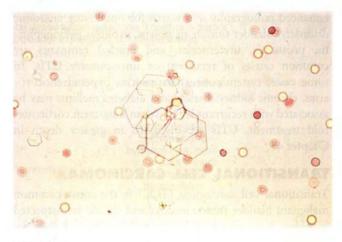
FIG 41-4
Dihydrate calcium oxalate crystals in urine sediment. These crystals are normally colorless. (From Grauer GF: Canine urolithiasis. In Allen DG, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)



FIG 41-5
Ammonium biurate crystals in urine sediment. These crystals are normally dark yellow. (From Grauer GF: Canine urolithiasis. In Allen DG, editor: Small animal medicine, Philadelphia, 1991, JB Lippincott.)

submitted for bacterial culture. This is because urine may be sterile in dogs and cats that have previously been treated with antibiotics, whereas the stone or bladder mucosa may still harbor bacteria.

The animal's signalment, as well as the clinicopathologic and radiographic findings, are often helpful in determining the type of urolith (Box 41-1); however, a quantitative urolith analysis should be performed if uroliths are passed or removed surgically. Identification of the urolith type facilitates the use of specific measures to dissolve them or prevent their recurrence. Qualitative commercial kit analysis of uroliths is not recommended because these kits do not detect silicic acid salts, frequently fail to detect calcium-containing uroliths, and yield false-positive results for uric acid more than half of the time in animals with cystine uroliths. Quan-



Cystine crystals in urine sediment. These crystals are normally clear to light yellow. (From Grauer GF: Canine urolithiasis. In Allen DG, editor: *Small animal medicine*, Philadelphia, 1991, JB Lippincott.)

titative urolith analysis, available at most teaching hospitals and reference laboratories, is recommended instead.

Urolithiasis is discussed in greater detail in Chapters 46 and 47.

# FELINE LOWER URINARY TRACT DISEASE (LUTD)

Cats with LUTD (often referred to as feline urologic syndrome, feline lower urinary tract inflammation, or feline interstitial cystitis; see Chapter 47) usually are presented because of pollakiuria, dysuria-stranguria, microscopic or gross hematuria, or inappropriate voiding. In male cats with a urinary tract obstruction, the presenting signs depend on how long the obstruction has been present. Within the first 6 to 24 hours, most obstructed cats will make frequent attempts to urinate, pace, vocalize, hide under beds or behind couches, lick their genitalia, and display anxiety. If the obstruction is not relieved within 36 to 48 hours, characteristic clinical signs of postrenal azotemia and hyperkalemia, including anorexia, vomiting, dehydration, depression, weakness, collapse, stupor, hypothermia, acidosis with hyperventilation, or bradycardia, may be observed. Sudden death may also occur.

On physical examination an unobstructed cat is apparently healthy, except for a small, easily expressible bladder. The bladder wall may be thickened, and palpation may cause the animal to void. Abdominal palpation may be painful to the unobstructed cat; however, the obstructed cat will always resent manipulation of the caudal abdomen unless it is severely depressed or comatose. The most significant physical examination finding in an obstructed cat is a turgid, distended bladder that is difficult or impossible to express. Care should be exercised in manipulating the distended bladder, however, because the wall has been injured by the increased intravesical pressure and is susceptible to rupture. In a male cat with a urethral obstruction, the penis may be



BOX 41-1

# Factors That May Aid in the Identification of Uroliths in Dogs

#### Struvite

- 80% to 97% of uroliths in female dogs are struvite.
- Uroliths in dogs younger than 1 year of age are usually struvite.
- There is a high incidence of concurrent urinary tract infection (especially Staphylococcus or Proteus spp.).
- · Urine is usually alkaline.
- Uroliths are radiodense.
- Increased prevalence in Miniature Schnauzers, Miniature Poodles, Bichon Frises, Cocker Spaniels.

#### **Calcium Oxalate**

- Increased prevalence in older male dogs (especially Miniature Schnauzers, Miniature Poodles, Yorkshire Terriers, Lhasa Apsos, Bichon Frises, and Shih Tzus).
- Urine is usually acidic to neutral.
- Uroliths are radiodense.
- Hypercalcemia may be a contributing factor.

#### **Ammonium Acid Urate**

Increased prevalence in male dogs (especially Dalmatians and Bulldogs).

- Urine is usually acidic to neutral.
- Uroliths are relatively radiolucent.
- Increased incidence in dogs with severe hepatic insufficiency (e.g., portosystemic shunts in Miniature Schnauzers and Yorkshire Terriers).

#### Silicate

- Increased prevalence in male dogs (especially German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers).
- · Urine is usually acidic to neutral.
- Urolith radiodensity is variable.
- High dietary intake of silicates probably predisposes (corn gluten and soybean hulls).

#### Cystine

- Increased prevalence in male dogs (especially Dachshunds, Basset Hounds, Bulldogs, Yorkshire Terriers, Irish Terriers, Chihuahuas, Mastiffs, and Rottweilers).
- Urine is usually acidic.
- Urolith radiodensity is variable.

congested and it may protrude from the prepuce. Occasionally, a urethral plug is seen extending from the urethral orifice, and in some cases the cat may lick its penis until it becomes excoriated and bleeds.

A history of acute onset of pollakiuria, dysuriastranguria, and hematuria in an otherwise healthy cat indicates LUTD. Physical examination should include digital rectal palpation of the caudal bladder and urethra in an attempt to determine whether there are masses or calculi, as well as abdominal palpation of the bladder before and after voiding to determine the residual urine volume and whether there are intraluminal masses or uroliths. The minimal diagnostic workup in cats with pollakiuria and dysuria-stranguria should always include a complete urinalysis. The urine should preferably be obtained by cystocentesis; however, if manipulation of the bladder during abdominal palpation results in voiding, a sample obtained from a clean tabletop may be used to assess urine pH and sediment.

An extensive diagnostic evaluation of the unobstructed cat is usually not warranted. In most of these cases the urine is bacteriologically sterile, and clinical signs respond to canned food dietary therapy. However, if clinical signs persist beyond 5 to 7 days of instituting dietary therapy, a second urinalysis with a urine culture and sensitivity, radiography of the abdomen, ultrasonography, and/or contrast-enhanced cystography-urethrography should be performed (Fig. 41-7).

# **HEMATURIA**

Hematuria, the presence of red blood cells in the urine, is frequently encountered in clinical veterinary medicine.

Because the urine strip reagents detect hemoglobin and myoglobin, a positive "blood" test in a urine dipstick does not necessarily mean that the patient has hematuria, and the sediment should be evaluated microscopically (discussed in more detail later). Hematuria occurring in conjunction with pollakiuria and dysuria-stranguria is usually associated with LUTI. Conversely, hematuria that occurs in the absence of other clinical signs often originates from the upper urinary tract. Hematuria may be gross (macroscopic hematuria) or occult (microscopic hematuria). Occult hematuria (more than five red blood cells per high-power field) is often present in dogs and cats with pollakiuria and dysuria-stranguria. The diagnostic workup in dogs and cats with hematuria is directed toward identifying the origin of the hemorrhage as well as the underlying disease.

In most cases hematuria is caused by inflammation, trauma, or neoplasia of the urogenital tract; however, hematuria may also be caused by systemic bleeding disorders, strenuous exercise, heat stroke, or renal infarcts. The renal telangiectasia that occurs in Cardigan Welsh Corgis may also cause hematuria, as can the renal hematuria in Weimaraners. The timing of gross hematuria during voiding may provide clues as to the source of the hemorrhage. Hematuria that occurs at the beginning of voiding (initial hematuria) is suggestive of hemorrhage originating from the lower urinary tract (bladder neck, urethra, vagina, vulva, penis, or prepuce). Extraurinary causes such as proestrus, metritis, pyometra, prostatic disease, or neoplasia of the genital tract may also cause initial hematuria (Table 41-2). Hematuria that occurs at the end of voiding (terminal hematuria) usually results

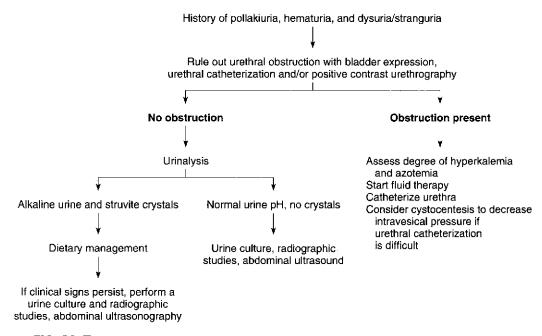


FIG 41-7
Diagnostic plan for feline lower urinary tract inflammation syndrome.



# Potential Causes of Hematuria

## **URINARY CAUSES**

# **EXTRAURINARY CAUSES**

# Initial hematuria

Urethral causes

Trauma Infection Urolithiasis

Neoplasia

Granulomatous urethritis Bladder trigone region

Neoplasia

Spontaneous bleeding unassociated with voiding may also occur with the following:

Prostatic: infection, cyst, abscess, tumor

Uterine: infection, tumor, proestrus, subinvolution

Vaginal: tumor, trauma

Preputial/penile: tumor, trauma

### Total or terminal hematuria

Pseudohematuria

Kidney, ureter, bladder

Infection Urolithiasis Tumor Parasitism

Trauma

Drug induced (cyclophosphamide)

Feline lower urinary tract inflammation syndrome

Renal infarct
Renal telangiectasia
Idiopathic renal hematuria

Prostatic (see above) Bleeding disorders Heat stroke Exercise-induced

from hemorrhage originating from the upper urinary tract (bladder, ureters, or kidneys). In this case the hemorrhage may be intermittent, which allows the red blood cells to settle in the bladder and be expelled with the last of the bladder contents. If hematuria occurs throughout voiding (total

hematuria), the hemorrhage usually originates in the bladder, ureters, or kidneys. Pseudohematuria may be caused by myoglobin or hemoglobin, drugs, and natural or artificial food dyes in the urine. In cases of pseudohematuria, the urine supernate remains discolored after centrifugation.

In dogs and cats with hematuria caused by inflammation, trauma, or neoplasia of the lower urinary tract, concurrent clinical signs usually include pollakiuria and dysuriastranguria. Hematuria associated with upper urinary tract disease may be associated with systemic signs, including depression, lethargy, anorexia, vomiting, diarrhea, weight loss, and abdominal pain, or it may be asymptomatic. In some cases upper urinary tract hemorrhage can result in the formation of blood clots in the bladder, leading to subsequent dysuria-stranguria. If hemorrhage from the genital tract is causing hematuria, spontaneous bleeding not associated with voiding may also be observed. Additional signs indicating that the genital tract is the source of hemorrhage include a purulent vaginal or urethral discharge independent of voiding, behavioral changes (e.g., proestrus), or straining to defecate in association with a stilted gait (e.g., prostatic

A complete physical examination often helps localize the source of the hematuria. If possible, the kidneys should be palpated and assessed in terms of their size, shape, consistency, and symmetry and for the presence of pain. The urinary bladder should be palpated before and after voiding, because, as already noted, a full bladder may obscure intraluminal masses, uroliths, or wall thickening. Observation of voiding should also be part of the physical examination and provides the opportunity to obtain a voided urine sample (Fig. 41-8). In addition, the timing of the hematuria can be confirmed and the character of the urine stream, as well as the presence or absence of dysuria, can be noted. Rectal palpation allows evaluation of the prostate in male dogs and of the pelvic urethra in dogs and cats of both sexes. The trigone region of the bladder can also be palpated rectally in small dogs and cats; this is facilitated by concurrent abdominal palpation, with the examiner pushing the bladder toward

the pelvic inlet. In larger female dogs digital vaginal palpation and the use of a vaginal speculum or scope allow for the urethral orifice to be evaluated; vaginal masses, strictures, and lacerations can be ruled in or out in this way. In male dogs the perineal urethra should be palpated subcutaneously from the ischial arch to the os penis, and the penis should be extruded from the prepuce and examined to determine whether there are masses, signs of trauma, or urethral prolapse. Finally, catheterization of the urethra in dysuric animals allows assessment of urethral patency; when indicated, positive contrast retrograde urethrography or ultrasonography can be employed to outline urethral anatomic abnormalities.

Comparison of urine obtained by cystocentesis with voided urine may help differentiate lower urinary tract or genital tract disease from upper urinary tract disease. Cystocentesis prevents the urine from being contaminated with bacteria, cells, and debris from the urethra, vagina, vulva, prepuce, or uterus; however, prostatic disease may alter the characteristics of urine obtained by cystocentesis (as a result of the reflux of fluid into the bladder). Abnormal urinalysis findings in urine collected by cystocentesis indicate involvement of the bladder, ureters, kidneys, or prostate. It should be remembered, however, that catheterization or bladder expression, and to a greater extent cystocentesis, may result in traumatic microscopic hematuria.

Urinalysis should be performed as soon as possible after urine collection. In addition to evaluating the urine sediment for red blood cells, the clinician should look for white blood cells, epithelial cells, tumor cells, casts, crystals, parasite ova, and bacteria. If urine remains at room temperature for more than 30 minutes, urease-producing bacteria can proliferate, resulting in an increase in the urine pH, which may cause red and white blood cells and casts to fragment

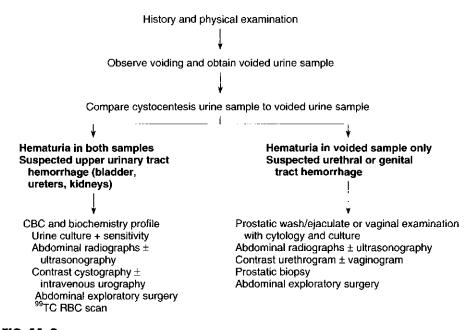


FIG 41-8

Diagnostic approach to dogs and cats with hematuria.

and lyse and may alter the crystal composition. In addition, hyposthenuria can result in the lysis of red and white blood cells, and lysed red blood cells in urine may create confusion between hemoglobinuria and hematuria. Refrigeration is the easiest way to preserve the stability of a urine sample. Although overnight refrigeration in a closed sterile container is acceptable for urine to be used for bacterial culture samples, it is not recommended for urine intended for chemical and cellular analysis.

Reagent strips used to detect blood in urine do so by detecting the peroxidase-like activity of hemoglobin from lysed cells. The test can detect approximately 0.05 to 0.3 mg of hemoglobin per deciliter of urine (equivalent to 10,000 lysed red blood cells per milliliter of urine, or approximately three lysed red blood cells per high-power field). These reagent test strips also show a positive reaction for blood in the presence of myoglobinuria.

A CBC and scrum biochemistry profile should be evaluated in dogs and cats with hematuria and concurrent systemic signs. An inflammatory leukogram is compatible with metritis-pyometra, acute bacterial pyelonephritis, or prostatitis. Azotemia occurring in association with hematuria usually indicates the presence of renal parenchymal disease or a rent in the urinary excretory pathway; however, prerenal causes of azotemia should also be ruled out. If the blood loss caused by hematuria is severe or if signs of generalized bleeding exist, a hemostasis profile, platelet count, and bleeding time should be evaluated (see Chapter 87).

Plain and contrast-enhanced radiography, ultrasonography, and/or cystoscopy will often help show the location and cause of hematuria. In some cases, abdominal exploratory surgery and biopsy may be necessary to arrive at a diagnosis. Biopsy specimens may be obtained from the kidneys, bladder, and prostate gland; if indicated, individual urcteral catheterization through a cystotomy or visualization through a cystoscope may be performed to determine if renal hematuria

is unilateral or bilateral. Nuclear medicine (technetiumlabeled red blood cells) can also be used to localize renal hematuria to one individual kidney.

# DISORDERS OF MICTURITION

Disorders of micturition include both urine retention and urine leakage (incontinence). Incontinence, the inappropriate passage of urine, may be caused by congenital abnormalities or acquired disorders. In evaluating an animal with incontinence, the clinician may find it helpful to determine whether the urinary bladder is distended, small, or normal in size (Table 41-3). Distended bladders are associated with urine retention and are usually caused by either detrusor hypocontractility or increased outflow resistance. Increased outflow resistance may be anatomic (e.g., urethral urolith) or functional (e.g., reflex dyssynergia). Urinary incontinence will occur with a primary urine retention disorder when intravesicular pressure overcomes outflow resistance pressure. This type of incontinence is termed paradoxic. More commonly, however, incontinence is associated with a small or normal-sized bladder that is typically caused by either decreased outflow resistance or increased detrusor contractility.

#### **Initial Evaluation**

The age of onset, reproductive status, age at neutering, current medications, and history of trauma or previous urinary tract disorders are important anamnestic points to cover when obtaining the history in an animal with disorders of micturition. The physical examination should include an evaluation of the perineum for evidence of urine scalding or staining. Thorough palpation of the bladder to assess its size and wall thickness and a rectal examination to assess anal tone, the prostate gland, the pelvic urethra, and the trigone region of the bladder should be performed in all cases. A



TABLE 41-3

Causes of Urinary Incontinence and Associated Clinical Signs

DISORDERS	CLINICAL SIGNS
Large bladder	
Lower motor neuron lesions	Dribbling of urine; distended bladder that is easily expressed; history of trauma or surgery in pelvic region
Upper motor neuron lesions	Distended bladder that is difficult to express; possible presence of paresis or paralysis
Reflex dyssynergia	Often, large-breed male dog; distended bladder that is difficult to express but easy to catheterize; urine stream initiated and then interrupted
Outflow tract obstruction	Usually male animals; dysuria-stranguria, dribbling of urine; distended bladder that is
Small bladder	difficult to express and catheterize
Urethral sphincter mechanism incompetence	Middle-aged or older neutered or spayed dogs; dribbling of urine usually occurring when animal is relaxed or asleep, normal voiding otherwise
Detrusor hyperreflexia/instability	Pollakiuria, dysuria-stranguria, hematuria, bacteriuria
Congenital abnormalities	Young animal; constant dribbling of urine possible, voiding possibly normal otherwise

digital vaginal examination is indicated, and vaginoscopy may be used to help identify congenital defects (e.g., vaginal strictures, ectopic ureters) in female dogs.

A neurologic examination should include evaluation of the perineal and bulbospongiosus reflexes. The perineal reflex causes the anal sphincter to contract and the tail to ventroflex in response to pinching of the perineal skin. The bulbospongiosus reflex causes the anal sphincter to contract in response to gentle compression of the bulb of the penis or the vulva. Both of these reflexes are dependent on an intact pudendal nerve (sensory and motor) and intact sacral spinal cord segments S1-S3. If both reflexes are normal, the pudendal reflex arc is intact. Because the pelvic nerve (sensory and motor parasympathetic innervation to the detrusor muscle) arises from the same sacral cord segments, damage to the pudendal nerve may also affect the pelvic nerve.

Dogs should be walked outside so that the voiding posture and urine stream size and character can be observed. Immediately after the animal has attempted to void, the bladder should be palpated to estimate the residual volume (normal residual volume is approximately 0.2 to 0.4 ml/kg). Catheterization to quantify the residual volume is indicated if a large bladder is palpable after voiding (in male dogs behavioral urine marking can make it difficult to assess the true residual urine volume).

A urinalysis should be performed in all animals with urinary incontinence. If a bacterial urine culture is indicated, as noted earlier, cystocentesis is the preferred method of collection; however, dogs and cats with a distended bladder should ideally be catheterized to empty the bladder and prevent the possibility of urine from leaking from the cystocentesis site.

# **Pharmacologic Testing and Treatment**

Frequently, the diagnosis of disorders of micturition (see Chapter 48) is based to some degree on the animal's response to pharmacologic testing and therapy. For example, detrusor hypocontractility should improve in response to a parasympathomimetic drug such as bethanechol, and urethral hypotonicity should respond to  $\alpha$ -adrenergic agents such as phenylpropanolamine or hormone replacement therapy. Urethral hypertonicity is treated with  $\alpha$ -sympatholytics (e.g., phenoxybenzamine) and striated muscle relaxants (e.g., diazepam). Detrusor hypercontractility often responds to treatment of the underlying inflammatory process (e.g., bacterial cystitis or urolithiasis); however, smooth muscle antispasmodics (e.g., oxybutynin) and parasympatholytics (e.g., propantheline) may be useful in cases of severe inflammation.

## DISTENDED BLADDER

Causes of incontinence that are typically associated with a distended bladder include neurogenic disorders (lower and upper motor neuron lesions and reflex dyssynergia) and urine outflow tract obstructive disorders (paradoxic incontinence; see Table 41-3). If neurologic lesions or deficits are detected during a neurologic examination, the status of the

bladder helps localize the lesion and classify the injury as an upper motor neuron (UMN) lesion (located above the fifth lumbar vertebral body) or a lower motor neuron (LMN) lesion (located at or below the fifth lumbar vertebral body). The most characteristic sign of an LMN lesion to the bladder is a distended bladder that is easily expressed. An LMN injury affecting innervation to the bladder creates both sphincter and detrusor hyporeflexia; if the lesion involves the S1-S3 spinal cord segments, both perineal and bulbospongiosus reflexes are absent.

Animals with UMN lesions to the bladder characteristically have a large, distended bladder that is difficult to express; the UMN lesion may also cause paresis or paralysis. Animals with a UMN lesion have no voluntary control of micturition, and the urethral sphincter shows reflex hyperexcitability because there is a lack of inhibition to the somatic efferents in the pudendal nerve, making expression of the bladder difficult. With time, UMN bladders may develop reflex contraction and partial emptying in response to detrusor stretching. This "automatic" emptying occurs without control or sensation.

Reflex dyssynergia or detrusor-urethral dyssynergia is a condition observed primarily in large-breed male dogs. The cause is usually difficult to determine but may include any of several neurologic lesions of the spinal cord or autonomic ganglia. Reflex dyssynergia results from active contraction of the detrusor without relaxation of the internal or external urethral sphincters. Characteristic signs of reflex dyssynergia include a normal or near-normal initiation of voiding, followed by a narrowed urine stream. Urine may be delivered in spurts, or flow may be completely disrupted and the animal will often strain to produce urine. After a while, the dog lowers his leg and then often begins dribbling urine as he walks away. Although it is difficult to express urine from the bladder of a dog with reflex dyssynergia, urethral catheterization is usually easy.

Incontinence in an animal with urinary outflow tract obstruction is called *paradoxic incontinence*. It occurs because intravesical pressure exceeds the pressure within the urethra, allowing urine to leak past the obstruction before a urethral or bladder rupture occurs. Clinical signs associated with an anatomic urethral obstruction include dribbling of urine, straining to urinate without producing urine, restlessness, and abdominal pain. The most common causes of urethral obstruction are calculi and neoplasia in dogs and urethral plugs in cats; however, urethral strictures and granulomatous urethritis can also create obstructions to urine flow. Prostatic disease in dogs may cause an outflow tract obstruction. Older male dogs with benign prostatic hyperplasia may be evaluated because of stranguria and tenesmus; however, prostatic neoplasia and prostatic abscess formation are more likely causes of urinary outflow tract obstruction in such animals.

# SMALL OR NORMAL-SIZED BLADDER

Causes of urinary incontinence in animals with a small or normal-size bladder include urethral sphincter mechanism incompetence (USMI), detrusor hyperreflexia or instability, and congenital abnormalities. Estrogen and testosterone are believed to contribute to the integrity of urethral muscle tone by increasing its responsiveness to  $\alpha$ -adrenergic innervation. Thus middle-aged to older, spayed female dogs are prone to the development of incontinence associated with decreased estrogen concentrations. This incontinence is most pronounced when the animal is asleep or relaxed and often responds to estrogen replacement therapy. Less frequently, incontinence develops in male dogs after castration; the condition seems to occur most commonly in dogs castrated at an older age and often responds to intramuscular testosterone administration. Diagnosis of both processes is based on the history, physical examination, and urinalysis findings (no evidence of LUTI) and on the response to therapy. Frequently, \alpha-adrenergic treatment (e.g., phenylpropanolamine) is effective in both male and female dogs with USMI incontinence, and in severe cases may be combined with hormone replacement treatment. Testosterone treatment is contraindicated in dogs that were neutered because of behavioral, prostatic, or perineal problems. In these cases  $\alpha$ -adrenergic treatment should be used; α-adrenergic treatment should be used with caution (or not at all) in patients wih hypertension.

Detrusor hyperreflexia or instability is the inability to control voiding because of a strong urge to urinate. Inflammation of the bladder or urethra may create a sensation of bladder fullness, which triggers the voiding reflex. Clinical signs of this type of incontinence include pollakiuria, dysuria-stranguria, and frequently hematuria. Bacterial UTI is the most common cause in the dog, and sterile LUTD is the most common cause in cats. A urinalysis that reveals evidence of UTI or inflammation (e.g., bacteriuria, pyuria, or hematuria) initially supports a tentative diagnosis of urge or inflammatory incontinence. If clinical signs persist after appropriate treatment for the urinary tract inflammation has been initiated, further diagnostic testing, including ultrasonography, contrast-enhanced radiography, and/or cystoscopy, are indicated because infiltrative disease of the bladder (e.g., neoplasia, chronic cystitis), polyps, uroliths, or urachal remnants can also result in pollakiuria and stranguria. It should also be noted that detrusor hyperreflexia/instability may also be a primary or idiopathic disorder that is not associated with bladder or urethral inflammation.

Urinary incontinence in a young animal may be associated with a variety of congenital defects of the urinary and genital systems. The most common defects are ectopic ureters and vaginal strictures, but a patent urachus, urethrorectal and urethrovaginal fistulas, and female pseudohermaphroditism have also been associated with urinary incontinence. Ectopic ureters are most commonly observed in female dogs. Breeds at high risk for ectopic ureters include Siberian Huskies, Miniature and Toy Poodles, Labrador Retrievers, Smooth Fox Terriers, West Highland White Terriers, Collies, and Cardigan Welsh Corgis. Ectopic ureters are rarely seen in cats, but the gender predisposition is reversed; the prevalence is higher in males than in females.

The most common clinical sign in an animal with ectopic ureters is a constant dribbling of urine, although dogs and cats with a unilateral ectopic ureter may void normally. Because 70% of ectopic ureters in dogs terminate in the vagina, vaginoscopy may allow visualization of the opening of the ectopic ureter; however, the opening can be difficult to see, even if the vagina is fully distended with air. Intravenous urography, retrograde vaginourethrography, and cystoscopy are additional diagnostic tests for characterizing the defect. In contrast to the incontinence associated with ectopic ureters, that associated with a vaginal stricture is often intermittent, occurring with changes in body position. Vaginal strictures can be diagnosed using digital vaginal examination, vaginoscopy, or contrast-enhanced vaginography.

Incontinence may also be caused by cognitive dysfunction, decreased bladder capacity, or decreased mobility in senior animals. Polyuric-polydipsic disorders such as chronic kidney disease and diabetes mellitus in senior animals also often exacerbate incontinence. Likewise, diuretic and corticosteroid therapy should be avoided in incontinent animals because of their negative effects on urine concentration.

#### POLYDIPSIA AND POLYURIA

Increased thirst and urine production are frequent presenting complaints in small animals. Polydipsia (PD) and polyuria (PU) in the dog and cat have been defined as a water consumption greater than 80 to 100 ml/kg/day and a urine production greater than 40 to 50 ml/kg/day, respectively. However, it is possible for thirst and urine production to be within the normal range and yet be abnormal in individual animals. Polydipsia and polyuria usually co-exist, and determining the primary component of the syndrome is one of the initial diagnostic considerations in an animal showing increased water consumption and urine production.

Thirst is stimulated primarily by osmotic factors. Hyperosmolality of the extracellular fluid usually occurs secondary to water loss, or it may result from the ingestion or intravenous infusion of hypertonic solutions. This hyperosmolality results in the dehydration of osmoreceptors, which stimulate thirst. Nonosmotic factors, including decreased arterial blood pressure, increased body temperature, pain, and certain drugs, can also stimulate thirst. Thirst is inhibited by expansion of the extracellular fluid volume, increased arterial blood pressure, drinking, and fullness of the stomach. Thirst is abnormally stimulated in animals with primary polydipsia, resulting in water consumption that exceeds physiologic need. Renal function in these animals is usually normal, and secondary polyuria occurs to rid the body of the excess water.

The kidneys maintain body fluid composition and volume by resorbing water and solutes from the glomerular filtrate. The resorption of solute in excess of water results in the formation of dilute urine. Conversely, the resorption of water in excess of solute results in the formation of concentrated urine. For concentrated urine to form, antidiuretic hormone (ADH) must be produced and released, and the renal tubules must be responsive to the ADH. For the latter to occur, the renal medullary interstitium must be hypertonic and at least one third of the total nephron population must be functional. ADH is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is stored in the posterior pituitary gland. Its release is stimulated by the same factors that stimulate thirst. In the presence of ADH, the distal portion of the distal convoluted tubule and the collecting duct become permeable to water, and water is resorbed from the tubular lumen. The hypertonicity of the renal medullary interstitium produces the osmotic pressure that drives the water resorption. A primary polyuria associated with a relative or absolute lack of ADH is termed central or pituitary diabetes insipidus (CDI), whereas a polyuria caused by nonresponsiveness to ADH is termed nephrogenic diabetes insipidus (NDI; Box 41-2).

Even though PU and PD usually occur together, the owner may not be aware of one or both components, depending on their severity and how closely the animal is observed. Conversely, owners frequently confuse pollakiuria with polyuria. Polyuria is often manifested by nocturia, pollakiuria and incontinence, whereas polydipsia is often manifested by a constantly empty water bowl and drinking from unusual sources, including toilets and puddles, and eating snow. It is relatively easy for most pet owners to measure 24-hour water consumption in a single-pet household, and this is a good way to confirm the presence of polydipsia; measuring water consumption in a multipet household is relatively difficult, unless the patient can be isolated.

A complete history and physical examination may suggest the underlying cause in animals with polydipsia and polyuria (Fig. 41-9); these include lymphadenopathy in dogs (lym-



#### Potential Causes of Polydipsia and Polyuria

# Primary Polydipsia

**Psychogenic** 

Hepatic insufficiency or portosystemic shunt

#### Primary Polyuria

Pituitary diabetes insipidus Nephrogenic diabetes insipidus Renal insufficiency or failure Hyperadrenocorticism Hypoadrenocorticism Hepatic insufficiency

Pyometra

Hypercalcemia

Hypokalemia

Postobstructive diuresis

Diabetes mellitus

Normoglycemic glucosuria

Hyperthyroidism

latrogenic or drug induced

Renal medullary solute washout

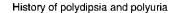
phoma with hypercalcemia); perineal mass (anal sac adenocarcinoma with hypercalcemia); cataracts (diabetes mellitus); symmetric truncal alopecia (hyperadrenocorticism); vaginal discharge (pyometra); and small, irregular kidneys (chronic kidney disease). A minimum workup consisting of a CBC, serum biochemistry profile, urinalysis, thoracic radiography, and abdominal radiography or ultrasonography may confirm or suggest a diagnosis in many animals with primary polyuria (e.g., hypercalcemia and mediastinal lymphadenopathy in dogs with lymphoma or increased serum alkaline phosphatase activity in dogs with hyperadrenocorticism). Frequently, further specific tests are necessary to confirm a diagnosis (e.g., lymph node aspiration or biopsy for lymphoma and an ACTH-stimulation test for hyperadrenocorticism [Table 41-4]).

The urine specific gravity may also be helpful in determining the underlying cause of the syndrome and in confirming whether the pet is actually polyuric. Urine specific gravity is usually divided into four ranges: hyposthenuric urine has a specific gravity of between 1.001 and 1.007; isosthenuric urine has the same specific gravity as plasma, 1.008 to 1.012; minimally concentrated urine has a specific gravity of between 1.013 and 1.030 in dogs and 1.013 and 1.035 in cats; and hypersthenuric urine has a specific gravity of more than 1.030 in dogs and more than 1.035 in cats. The animal's hydration status, serum urea nitrogen and creatinine concentrations, and current medications must be known in order to interpret random urine specific gravity values. For example, a normally hydrated dog may have a urine specific gravity in the isosthenuric range and a cat receiving furosemide may be somewhat dehydrated and still have minimally concentrated urine; however, normal dogs and cats should produce hypersthenuric urine in response to clinically detectable dehydration.

It is unusual for dogs and cats with PD and/or PU to have a urine specific gravity consistently in the hypersthenuric range; this finding warrants the measurement of water consumption to confirm if the patient actually has either condition. Animals with primary polydipsia or with CDI usually have urine specific gravities in the hyposthenuric range, whereas animals with nephrogenic diabetes insipidus are most likely to be isosthenuric or to have minimally concentrated urine. If the history, physical examination, and minimal diagnostic workup findings are unrewarding, specialized diagnostic tests, including determination of the plasma osmolality, gradual water deprivation testing, and determination of the animal's response to exogenous ADH, may be necessary to arrive at a diagnosis (see Chapter 42 and Fig. 41-9).

# **PROTEINURIA**

Normally, the urine of dogs and cats contains only a small amount of protein because the selective permeability of the glomerular capillary wall restricts the filtration of most plasma proteins on the basis of protein weight and charge.



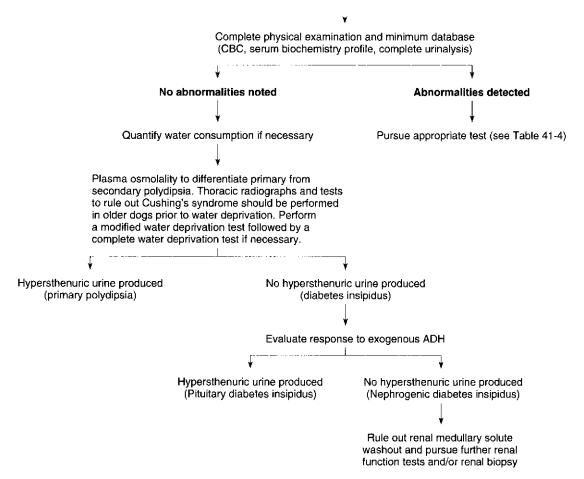


FIG 41-9
Diagnostic approach to dogs and cats with polydipsia and polyuria.



**TABLE 41-4** 

Ancillary Diagnostic Tests that May Be Used to Evaluate Dogs and Cats with Polydipsia and Polyuria

SUSPECTED DISORDER	FURTHER DIAGNOSTIC TESTS	
Primary polydipsia	Plasma osmolality, modified water deprivation, rule out hepatic insufficiency or PSS	
Pituitary diabetes insipidus	Plasma osmolality, modified water deprivation test, response to exogenous antidiuretic hormone	
Nephrogenic diabetes insipidus		
Renal insufficiency or failure	Serum urea nitrogen and creatinine concentrations, creatinine clearance, electrolyte fractional clearance, biopsy	
Hyperadrenocorticism	ACTH-stimulation test, dexamethasone-suppression test, urine cortisol/creatinine ratio	
Hypoadrenocorticism	Serum sodium/potassium ratio, ACTH-stimulation test	
Hepatic insufficiency or PSS	Serum bile acids preprandially and postprandially, abdominal ultrasonography : Doppler, <sup>99</sup> Tc scan (enema), portal angiography, biopsy	
Pyometra	Abdominal radiography or ultrasonography, vaginal cytology	
Hypercalcemia	Serum calcium concentrations (total and ionized), radiography, lymph node cytologi or biopsy, bone marrow cytology, PTH/PTHrp assays	
Hypokalemia	Serum potassium concentration, potassium fractional clearance	
Glucosuria	Obtain concurrent serum glucose concentration	
Hyperthyroidism	Serum total and free thyroxine concentrations, triiodothyronine-suppression test, cardia evaluation, 99Tc scanning	
Renal medullary solute washout	Repeat water deprivation and exogenous ADH testing after gradual water restriction and dietary salt and protein supplementation for 10 to 14 days	

ACTH, Adrenocorticotropic hormone; ADH, antidiuretic hormone; PSS, portosystemic shunt; PTH, parathyroid hormone; PTHrp, parathyroid hormone–related peptide.



**TABLE 41-5** 

Approximate Molecular Weights of Various Plasma Proteins

PLASMA PROTEIN	MOLECULAR WEIGHT (DALTONS)
Insulin Parathyroid hormone Lysozyme Myoglobin Growth hormone Bence Jones proteins (monomer) Amylase Hemoglobin Antithrombin Albumin	6,000 9,000 14,000 17,000 22,000 22,000 50,000 64,500 65,000 69,000
Immunoglobulin G Immunoglobulin A (dimer) Fibrinogen Immunoglobulin M	160,000 300,000 400,000 900,000

Proteins with a molecular weight greater than 60,000 to 65,000 daltons are normally not present in large quantities in normal glomerular filtrate (Table 41-5). The negatively charged glomerular capillary wall further impedes the passage of negatively charged proteins such as albumin. In addition, smaller-molecular-weight proteins, as well as those positively charged proteins that do pass through the glomerular capillary wall, are largely resorbed by the proximal tubular epithelial cells. Such resorbed proteins may be broken down and used by the epithelial cells or returned to the bloodstream, Renal proteinuria most commonly arises because of glomerular capillary wall lesions that allow increased filtration of plasma proteins into the glomerular filtrate. Tubular lesions that result in decreased reabsorption of filtered proteins (primarily albumin) are another source of renal proteinuria. Although glomerular lesions result in greater magnitude of proteinuria compared with tubular lesions, proteinuria associated with both types of lesions tends to be persistent and serves as an important marker of kidney

Proteinuria is routinely detected by semiquantitative methods, including the dipstick colorimetric test and the sulfosalicylic turbidimetric test. The dipstick test is inexpensive and easy to use; amino groups of proteins bind to the indicator incorporated in the filter paper on the dipstick and cause a color change. The color change is graded by comparing it to a standard, but the comparison is subjective. However, automated dipstick analyzers that use reflectance photometry to consistently read the color change and provide a printout of results are available (Idexx VetLab UA Analyzer, IDEXX Laboratories, Westbrook, Maine). The dipstick test is most sensitive to albumin because albumin has more free amino groups than globulins. False-positive results may be obtained if the urine is alkaline, if it has been contaminated

with quaternary ammonium compounds, or if the dipstick is left in contact with the urine long enough to leach out the citrate buffer that is incorporated in the filter paper pad. False-negative results may occur in the setting of Bence Jones proteinuria or dilute or acidic urine. The dipstick test can detect approximately 30 to 1000 mg of protein per deciliter. The dipstick method is not affected by urine turbidity; however, the supernatant from centrifuged urine samples should ideally be used for all physiochemical analyses.

The sulfosalicylic acid test is performed by mixing equal quantities of urine supernate and 3% to 5% sulfosalicylic acid, and subjectively grading the turbidity that results from precipitation of protein on a 0 to 4 scale. This test is also more sensitive to albumin than globulins, but Bence Jones proteinuria can be detected. False-positive results may occur if the urine contains radiographic contrast agents, penicillin, cephalosporins, sulfisoxazole, or the urine preservative thymol. The protein content may be overestimated with the sulfosalicylic acid test if uncentrifuged urine or turbid urine is analyzed. False-negative results may occur if the urine is markedly alkaline or diluted. Because the varying degrees of turbidity are not standardized, results may also vary among laboratories. This test can detect approximately 5 to 5000 mg of protein per deciliter. Further information on such tests is contained in Chapter 42.

Proteinuria detected by these semiquantitative methods should always be interpreted in light of the urine specific gravity and urine sediment. For example, a 2 proteinuria with a 1.010 urine specific gravity is suggestive of a much greater urine protein loss on a 24-hour basis than is a 2 proteinuria with a 1.040 urine specific gravity. Because the urine protein concentration is frequently increased in animals with LUTI or hemorrhage, proteinuria should also be assessed in the context of urine sediment changes indicative of inflammation or hemorrhage (e.g., bacteria and increased numbers of white and red blood cells and epithelial cells in the urine sediment). The evaluation of the animal with proteinuria is further discussed in Chapter 42.

Once persistent proteinuria has been documented, the next step is to identify its source. Proteinuria may be caused by physiologic or pathologic conditions (Table 41-6). Physiologic or benign proteinuria is often transient and abates when the underlying cause is corrected. Strenuous exercise, seizures, fever, exposure to extreme heat or cold, and stress are examples of conditions that may cause physiologic proteinuria. The pathophysiology of physiologic proteinuria is not completely understood; however, relative renal vasoconstriction, ischemia, and congestion are thought to be involved. Decreased physical activity may also affect urine protein excretion in dogs; one study showed that urinary protein loss is higher in dogs confined to cages than in dogs with normal activity. This is different from the postural or orthostatic proteinuria that occurs in people. In the latter condition, mild proteinuria occurs when the person is standing or active but diminishes when the person is recumbent.

Pathologic proteinuria may be caused by urinary or nonurinary abnormalities. Nonurinary disorders associated



TABLE 41-6

#### Classification of Proteinuria

TYPE	CAUSES
Physiologic	Strenuous exercise
	Seizures
	Fever
	Exposure to heat or cold
	Stress
	Decreased activity level (strict cage rest)
Pathologic	-
Nonurinary	Bence Jones proteinuria
•	Hemoglobinuria or myoglobinuria
	Congestive heart failure
	Genital tract inflammation
Urinary	
Nonrenal	Cystourolithiasis
	Bacterial cystitis
	Trauma or hemorrhage
	Neoplasia
	Drug-induced cystitis (e.g.,
	cyclophosphamide)
Renal	Glomerular lesions
	Abnormal tubular resorption
	Renal parenchymal inflammation or
	hemorrhage
	₹

with proteinuria often involve the production of small-molecular-weight proteins that are filtered by the glomeruli and that subsequently overwhelm the resorptive capacity of the proximal tubule. Examples of this include the production of immunoglobulin light chains (Bence Jones proteins) by neoplastic plasma cells or lymphocytes and the release of hemoglobin from damaged red blood cells, which then exceeds the binding capacity of haptoglobin (in this case centrifuged urine would be discolored by the pigment). Renal congestion secondary to congestive heart failure can also result in pathologic nonurinary proteinuria, as can genital tract inflammation (e.g., prostatitis or metritis).

Pathologic urinary proteinuria may be renal or nonrenal in origin. Nonrenal proteinuria most frequently occurs in association with LUTI or hemorrhage. Changes seen in the urine sediment usually reflect the underlying cause (e.g., urolithiasis, neoplasia, trauma, bacterial cystitis). On the other hand, renal proteinuria is most often caused by glomerular lesions. Glomerulonephritis and amyloidosis alter the selective permeability of the glomerular capillaries and frequently result in a proteinuria greater than 50 mg/kg/24 h or urine protein: creatinine ratios greater than 2.0 (see Chapter 42). The occurrence of persistent proteinuria with a normal urine sediment or accompanied by hyaline cast formation is strongly suggestive of glomerular disease. Besides glomerular disease, renal proteinuria may be caused by inflammatory or infiltrative disorders of the kidney (e.g., neoplasia, pyelonephritis) or by tubular abnormalities that

result in the decreased resorption of filtered protein (e.g., Fanconi's syndrome and chronic kidney disease).

Prerenal (physiologic and pathologic—nonurinary) and postrenal (pathologic urinary—nonrenal) proteinuria, as well as inflammatory renal proteinuria, can usually be identified on the basis of history and physical examination findings and the urine sediment changes. Renal proteinuria caused by abnormal tubular resorption may be accompanied by normoglycemic glucosuria and an abnormal urinary loss of electrolytes, which can help differentiate tubular from glomerular proteinuria. It is important to identify the source of the proteinuria because the quantification of renal proteinuria can be a helpful prognostic tool, although it is not useful in animals with prerenal or postrenal proteinuria.

# **AZOTEMIA**

Azotemia is defined as increased concentrations of urea and creatinine (and other nonproteinaceous nitrogenous substances) in the blood. The interpretation of serum urea nitrogen and creatinine concentrations as a measure of renal function requires a knowledge of the production and excretion of these substances. Urea is synthesized in the liver from ammonia, which is in turn generated from the catabolism of ingested and endogenous proteins. Urea production is increased in the settings of a high dietary protein intake, upper gastrointestinal tract hemorrhage, and catabolic states that result in the breakdown of body proteins (e.g., fever and corticosteroid administration). Conversely, urea production is decreased in the settings of a low dietary protein intake, use of anabolic steroids, decreased hepatic function, or decreased delivery of ammonia to the liver (e.g., portosystemic shunt). Urea has a small molecular weight (60 daltons) and is a permeate solute that readily diffuses throughout all body fluid compartments; its concentration is similar in intracellular and extracellular fluid and in plasma, serum, and blood. Urea that diffuses into the intestinal lumen is degraded by enteric organisms to ammonia, which is then reabsorbed into the portal circulation and again converted to urea by the liver. Urea is principally excreted by the kidneys; it is freely filtered through the glomeruli and passively resorbed by the renal tubules. The tubular resorption of urea is increased and the net excretion decreased when tubular flow rates and volumes are decreased, as it occurs in patients with dehydration. Conversely, the tubular resorption of urea is decreased and the excretion is increased in the presence of diuresis. Decreased renal blood flow (prerenal causes, such as dehydration or decreased cardiac output) and decreased excretion of urine (postrenal causes, such as urethral obstruction or ruptured bladder), as well as primary renal dysfunction, will result in decreased excretion of urea.

Creatinine is irreversibly formed by the nonenzymatic metabolism of creatine and phosphocreatine in muscle. Creatinine production is relatively constant and proportional to muscle mass; animals with a large muscle mass produce more creatinine each day than do animals with a small muscle mass. For example, serum creatinine concentration in Greyhounds is higher than in dogs of other breeds. Muscle trauma and inflammation do not increase the production of creatinine. In comparison with the urea nitrogen concentration, the creatinine concentration is relatively unaffected by the dietary protein level; however, serum creatinine concentrations can increase after the ingestion of meat and the subsequent increased absorption of creatinine from the gastrointestinal tract. The molecular weight of creatinine is 113 daltons; therefore it diffuses throughout body fluid compartments more slowly than urea does. Some creatinine diffuses into the intestinal lumen, is degraded by enteric bacteria, and is excreted from the body in the feces; however, most creatinine is excreted by the kidneys. Creatinine is freely filtered by the glomeruli and is not significantly resorbed or secreted by the renal tubules. Because the production of creatinine is relatively constant, an increase in the serum creatinine concentration is indicative of decreased renal excretion. It is important to remember, however, that prerenal and postrenal factors influence renal function and, therefore, the excretion of creatinine. Disproportionate increases in blood urea nitrogen (BUN) relative to creatinine can be caused by high-protein diets, upper gastrointestinal hemorrhage, and increased tubular reabsorption of urea nitrogen associated with prerenal azotemia. Conversely, a disproportionately low BUN can be observed with decreased liver function, portosystemic shunts, low-protein diets, and prolonged diuresis.

Rule outs for azotemia include prerenal, renal, and postrenal causes. Any condition that causes a decrease in renal blood flow may result in prerenal azotemia, and this includes hypovolemia (e.g., dehydration, hypoadrenocorticism), hypotension (e.g., anesthesia, cardiomyopathy), and aortic or renal arterial thrombus formation. Initially, the kidneys are structurally and functionally normal in dogs and cats with prerenal azotemia, and they respond to the decreased renal blood flow by conserving water and sodium. Hypersthenuric urine (i.e., specific gravity greater than 1.030 in dogs and greater than 1.035 in cats) with a relatively low concentration of sodium and a high concentration of creatinine is produced (Table 41-7). Elimination of the underlying disorder (e.g., fluid therapy to correct hypovolemia) results in rapid resolution of the azotemia unless the underlying disorder has persisted long enough or is severe enough to have caused renal parenchymal damage.

Postrenal azotemia is usually caused by an obstruction to urine outflow or a rupture of the urine outflow tract. Similar to prerenal azotemia, in postrenal azotemia the kidneys are initially normal; however, the urine specific gravity varies depending on the animal's hydration status. In patients with urethral obstruction, catheterization is difficult and dysuria and stranguria are common clinical signs. Rupture of the urinary tract that results in azotemia usually involves the bladder or urethra, is more common in male than female animals, and frequently results in abdominal effusion or subcutaneous fluid accumulation. Fluid obtained by abdominocentesis is usually sterile and contains a higher concentration of creatinine than the serum does. Even though creatinine is a small molecule and equilibrates rapidly, the concentration of creatinine in the abdominal fluid is higher than that of serum if the kidneys are producing urine that is draining into the abdomen. Positive contrast-enhanced urethrography or cystography is the best way to confirm a rupture of the urethra or bladder.

Renal azotemia occurs as a result of nephron loss or damage. A diagnosis of renal azotemia is confirmed if the azotemia is persistently associated with isosthenuria or minimally concentrated urine (see Table 41-7). Inasmuch as urine is usually stored in the bladder for several hours, it is important not to evaluate the specific gravity of urine produced before the onset of the azotemia. For example, prerenal azotemia may occur in response to acute, severe dehydration; however, the animal may appear to have renal azotemia if the hypersthenuric urine being produced in response to the dehydration is diluted by a larger volume of previously formed, less concentrated urine. The differentiation of prerenal from renal azotemia can be a diagnostic challenge in some animals. Prerenal dehydration causing azotemia and accompanied by a decreased urineconcentrating ability can be confused with renal azotemia. Examples of conditions that can cause this syndrome include furosemide treatment, which causes dehydration, and hypercalcemia, which compromises the urine-concentrating ability and results in dehydration secondary to vomiting. Although fluid therapy is often implemented initially in animals with either prerenal or renal azotemia to manage the dehydration, the prognosis is quite different. Frequently, the response to fluid therapy is the best way to differentiate prerenal from renal azotemia; renal azotemia does not completely resolve in response to fluid therapy alone.

	TABLE	41-7
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Differentiation of Prerenal Azotemia from Acute Renal Failure

INDICES	PRERENAL AZOTEMIA	ACUTE RENAL FAILURE
Urine specific gravity Fractional clearance of sodium	Hypersthenuric	Isosthenuric or minimally concentrated >2%
$\label{eq:continuous} \begin{tabular}{ll} $\{Urine_{N\alpha} \times Serum_{Cr}/\{Urine_{Cr} \times Serum_{N\alpha}\}$ \\ $Urine\ creatinine-to-serum\ creatinine\ ratio \end{tabular}$	>20:1	<10:1



Differentiation of Acute from Chronic Renal Failure on the Basis of History, Clinical Signs, and Clinical Pathology Data

#### **Acute Renal Failure**

History of ischemia or toxicant exposure
Normal or increased hematocrit
Enlarged kidneys
Hyperkalemia (with oliguria)
More severe metabolic acidosis
Active urine sediment
Good body condition
Relatively severe clinical signs for level of dysfunction

### Chronic Renal Failure

History of renal disease or polydipsia-polyuria
Nonregenerative anemia
Small, irregular kidneys
Normal or hypokalemia
Normal or mild metabolic acidosis
Inactive urine sediment
Weight loss
Relatively mild clinical signs for level of dysfunction

Renal failure is a state of decreased renal function in which azotemia and the inability to produce hypersthenuric urine persist concurrently. The treatment and prognosis vary for animals with acute renal failure and chronic kidney disease; therefore it is important to distinguish between these two entities. Acute renal failure (ARF) develops within hours or days. Unique clinical signs and clinicopathologic findings often associated with ARF include enlarged or swollen kidneys, hemoconcentration, good body condition, an active urine sediment, relatively severe hyperkalemia and metabolic acidosis, and relatively severe clinical signs for the degree of azotemia (Box 41-3). Chronic kidney disease (CKD) develops over a period of weeks, months, or years, and the clinical signs are often relatively mild for the magnitude of azotemia. Unique signs of CKD often include a history of weight loss and PD/PU, poor body condition, nonregenerative anemia, small and irregular kidneys, and osseous fibrodystrophy caused by secondary renal hyperparathyroidism (see Box 41-3).

#### RENOMEGALY

Renal enlargement is usually detected by physical examination or by abdominal imaging. A quick rule of thumb is that the kidney length on abdominal radiographs should be approximately equivalent to 2.5 to 3 times the length of the second lumbar vertebra in cats and 2.5 to 3.5 times the length of the second lumbar vertebra in dogs. Enlarged kidneys with a normal shape can be caused by edema, acute inflammation, diffusely infiltrating neoplastic disease, unilateral compensatory hypertrophy, trauma (intracapsular hemorrhage), perirenal cysts, or hydronephrosis. Enlarged, abnormally shaped kidneys may be caused by renal neoplasia, cysts, abscesses, hydronephrosis, or hematomas. Ultrasonography, intravenous urography, and advanced imaging (CT scan or magnetic resonance imaging) can be used to further define kidney shape and reveal internal details. Ultrasonography is particularly useful for evaluating enlarged kidneys associated with fluid accumulation (e.g., hydronephrosis, abscesses, and perirenal and parenchymal cysts) and can also be used to guide fine-needle aspiration or needle biopsy of the affected kidney. Kidney biopsy is often necessary to confirm the cause of the renomegaly; however, biopsy is contraindicated if only one kidney is present or if a bleeding disorder, hydronephrosis, a cyst, or an abscess is suspected.

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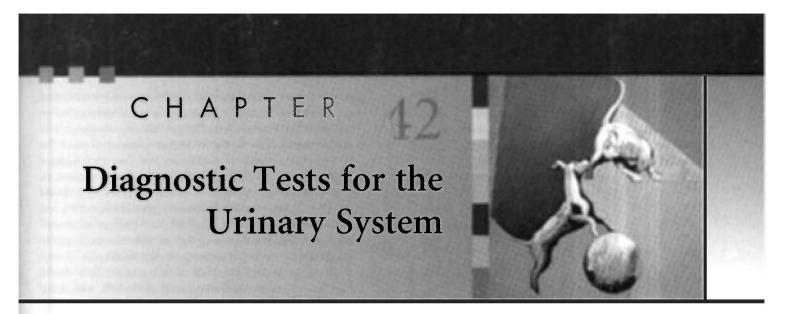
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# CHAPTER OUTLINE

RENAL EXCRETORY FUNCTION
Glomerular Filtration Rate
Fractional Clearance
QUANTIFICATION OF PROTEINURIA
PLASMA AND URINE OSMOLALITY, WATER
DEPRIVATION TEST, AND RESPONSE TO
EXOGENOUS ANTIDIURETIC HORMONE
BLADDER AND URETHRAL FUNCTION
BACTERIAL ANTIBIOTIC SENSITIVITY TESTING
DIAGNOSTIC IMAGING
CYSTOSCOPY
RENAL BIOPSY

#### RENAL EXCRETORY FUNCTION

#### **GLOMERULAR FILTRATION RATE**

Blood urea nitrogen (BUN) and creatinine concentrations provide a crude index of the glomerular filtration rate (GFR). However, inasmuch as the creatinine concentration is influenced by fewer extrarenal variables and creatinine is not resorbed by the renal tubules, the serum creatinine concentration is a better index of GFR than is the BUN. Nevertheless, azotemia resulting from impaired renal function is not detectable until approximately three fourths of the nephrons in both kidneys are nonfunctional. This percentage may be even higher in dogs and cats with chronic progressive renal disease because the remaining viable nephrons often undergo compensatory hypertrophy. Therefore renal clearance and measurement of GFR can provide more accurate information about renal excretory function than the serum creatinine and BUN concentrations, especially early in renal disease, before three fourths of the nephrons have been destroyed.

Renal clearance is the rate at which a substance is completely cleared from a certain volume of plasma. Substances used to measure renal clearance must be freely filtered by the glomerulus (not protein-bound) and not affected by tubular resorption or secretion or by metabolism elsewhere in the body. In addition, the substance used must not alter renal function. The renal clearance of inulin is the gold standard method of determining GFR, but it is difficult to measure the inulin concentration in plasma and urine. On the other hand, it is relatively easy to determine the renal clearance of creatinine and therefore more practical. The renal clearance of creatinine can be calculated by multiplying the concentration of creatinine in urine by the rate of urine production and then dividing the product by the serum concentration of creatinine, as follows:

Volume of plasma cleared  $(ml/min) = GFR (ml/min) = (Urine_{Cr}[mg/dl] \times Urine volume [ml/min)] = Serum_{Cr} (mg/dl)$ 

For example, if the urine creatinine concentration is 60 mg/dl, urine production is 3 ml/min, and the serum creatinine concentration is 1.8 mg/dl, 100 ml of plasma is cleared of creatinine per minute. This value is divided by the animal's body weight in kilograms and expressed in milliliters per minute per kilogram. Note that prerenal and postrenal factors, as well as renal parenchymal lesions, influence plasma clearance.

The GFR can be calculated using the clearance of either endogenous or exogenous creatinine. Endogenous creatinine clearance, however, requires urine collection for a lengthy period (i.e., 24 hours) to minimize errors in the collection, thus necessitating the use of indwelling catheters, repeated urinary catheterization, or the use of metabolism cages for urine collection. Endogenous creatinine clearance can be used in the clinical setting to evaluate renal excretory function if renal dysfunction is suspected, but the serum urea nitrogen and creatinine concentrations are within normal ranges. In early renal disease, a relatively large decline in GFR results in small changes in serum creatinine concentrations within the normal range. Less commonly, endogenous creatinine clearance can be used to better quantify renal excretory function in animals with azotemia because in advanced renal disease relatively large changes in serum creatinine concentrations are accompanied by much smaller decreases in GFR. A serum sample obtained approximately midway through the urine collection period and a well-mixed aliquot



BOX 42-1

Calculation of Endogenous Creatinine Clearance, 24-Hour Urine Protein Excretion, and Urine Protein/ Creatinine Ratio

#### Data

Body weight = 20 kg 24-hour urine volume = 400 ml (4.0 dl) Urine protein concentration = 650 mg/dl Urine creatinine concentration = 110 mg/dl Serum creatinine concentration = 1.9 mg/dl Time—24 hours = 1440 minutes

#### Calculations

Endogenous creatinine clearance =  $\frac{\{Urine_{Cr}\} \times \{Urine \ volume\}}{\{Serum_{Cr}\} \times \{Time\} \times \{Body \ weight\}}, \text{ or } \\ \frac{(110 \ mg/dl) \times (400 \ ml)}{\{1.9 \ mg/dl\} \times (1440 \ min) \times (20 \ kg)} = \\ 0.8 \ ml/min/kg$ 

24-hour urine protein excretion =

$$\frac{(650 \text{ mg/dl}) \times (4.0 \text{ dl})}{(20 \text{ kg})} = 130 \text{ mg/kg}$$

#### Data

Urine protein from random urine sample = 750 mg/dl Urine creatinine from random urine sample = 120 mg/dl

#### Calculation

Urine protein/creatinine ratio = (750 mg/dl)/(120 mg/dl) = 6.25 6.25 × 20 (linear regression conversion factor) = 125 mg of urine protein/kg/24 hours

from the 24-hour urine sample are used to measure creatinine concentrations. The volume of urine collected is divided by 1440, the number of minutes in 24 hours (Box 42-1). One drawback to this method, however, is the fact that noncreatinine chromogens present in the serum falsely increase serum creatinine concentrations if the standard alkaline picrate method of analysis is used, especially when serum creatinine concentrations are within the normal range or only mildly increased. In fact, noncreatinine chromogens can account for as much as 50% of the total amount of chromagens in animals with serum creatinine concentrations within normal ranges. Because noncreatinine chromogens are not excreted in the urine, the calculated endogenous creatinine clearance can be falsely decreased. Despite this problem, endogenous creatinine clearance has been shown to closely approximate inulin clearance in dogs and cats. Normal values for endogenous creatinine clearance in the dog and cat are 2.8 to 3.7 and 2 to 3 ml/min/kg, respectively.

The clearance of exogenous creatinine can be determined over a relatively short period, and because the serum creatinine concentration is considerably increased, the effect of

noncreatinine chromogens is largely negated. Measurement of exogenous creatinine clearance is most appropriate in nonazotemic animals. Initially, a constant intravenous infusion of creatinine was used in the test; however, research has shown that a single subcutaneous injection of 100 mg of creatinine per kilogram of body weight (Sigma Chemicals, St. Louis, Missouri) can be used instead. Urine is collected for 20 minutes, starting 40 minutes after the injection, and serum samples are obtained at the start and end of the collection period (the average of the two serum creatinine concentrations is used to calculate creatinine clearance). Because of the short collection period, it is important to rinse the bladder with a sterile saline solution at the start and end of the collection. To increase the accuracy of this technique, two 20-minute clearances can be calculated and averaged. Normal exogenous creatinine clearance values are 3.5 to 4.5 ml/min/ kg in dogs and 2.4 to 3.3 ml/min/kg in cats.

Plasma clearance of iohexol, an iodinated radiographic contrast agent, has been shown to reliably estimate GFR in dogs and cats. Because calculation of iohexol clearance does not require urine collection, the procedure is less labor intensive and invasive compared with creatinine clearance. Iohexol plasma clearance can be performed in dogs and cats that are well hydrated and fasted for 12 hours before the study. Iohexol (e.g., Omnipaque 240 mg I/ml, available from GE Healthcare, Inc., Princeton, NJ) is administered intravenously at the dosage of 300 mg iodine/kg body weight. Blood samples are collected at 2, 3, and 4 hours after the intravenous (IV) injection. Serum from each blood sample is harvested (approximated 1.5 ml of serum is needed per sample) and then shipped either chilled or frozen to the university teaching hospital or specialized reference laboratory (e.g., Diagnostic Center for Population and Animal Health, Toxicology Section, Michigan State University).

Renal scintigraphy using technetium 99m-labeled diethylenetriaminepentaacetic acid also allows the GFR to be evaluated and is available at several universities and major referral centers. This is a quick, noninvasive method that does not require urinary catheterization and has the advantage of being able to quantitatively evaluate individual kidney function. Disadvantages of this procedure include its limited availability, exposure of the animal to radioisotopes, the need for radioisotope disposal, and poorer correlation with inulin clearance when compared with plasma clearance techniques such as that used with iohexol.

#### FRACTIONAL CLEARANCE

The clearance of various solutes in the urine may be compared with the clearance of creatinine in the urine to assess the degree of tubular resorption or secretion. Because the renal clearance of creatinine is relatively constant over time, expressing the renal clearance of a solute as a percentage of the clearance of creatinine gauges the body's attempt to conserve or excrete the solute. The fractional clearance (FC) of a solute is the quotient of the urine: serum solute ratio divided by the urine: serum creatinine ratio ([Urine<sub>S</sub>: Serum<sub>S</sub>]/[Urine<sub>Gr</sub>: Serum<sub>Gr</sub>]). A timed urine collection is not

necessary to determine the FC of a solute. Some solutes, including glucose and amino acids, are normally highly conserved, whereas electrolytes such as sodium, chloride, potassium, calcium, and phosphorus are variably conserved. In normal dogs and cats the FCs of sodium, chloride, and calcium are less than 1%; however, the FCs of potassium and phosphorus are more variable and may be as high as 20% and 39%, respectively. Examples of situations in which a knowledge of the FC of electrolytes may be helpful include (1) the diagnosis of primary hyperparathyroidism, in which the FC of phosphorus is increased; (2) the diagnosis of tubular dysfunction, such as Fanconi's syndrome, in which the FCs of all electrolytes are increased; and (3) the differentiation of prerenal azotemia, in which the FC of sodium is decreased, from acute renal failure, in which the FC of sodium is increased (>2%; see Table 41-3). In many cases, however, the correlation between spot urine sample and 24hour urine sample FC is poor. In addition, the amount of dietary intake of the electrolyte in question can influence results, and there tends to be large intrapatient and interpatient variation in results. Moreover, the FC may also be breed dependent; for example, FC of most electrolytes is significantly different in Greyhounds than in other dog breeds. For these reasons, the clinical usefulness of FC of electrolytes is limited.

# **QUANTIFICATION OF PROTEINURIA**

If the results of the dipstick or sulfosalicylic acid test for proteinuria (see Chapter 41) indicate the presence of persistent proteinuria and the urine sediment examination findings are normal (i.e., renal proteinuria is suspected), urine protein excretion should be quantified. This helps in evaluating the severity of renal lesions and assessing the response to treatment or the progression of disease. The trichloroacetic acid-N-Ponceau S, Coomassie brilliant blue, or benzethonium chloride tests are the most common methods used to quantify urine protein and are available at referral centers and reference laboratories.

The urine protein: creatinine ratio in canine and feline urine samples has been shown to accurately reflect the quantity of protein excreted in the urine over a 24-hour period. Both urine creatinine and urine protein concentrations are affected by urine volume and urine concentration, but the ratio of the urine protein to urine creatinine is not. This allows quantitation of proteinuria without the need to collect a timed urine sample, and therefore the test has greatly facilitated the diagnosis of kidney disease in small animals. A urine protein; creatinine ratio of less than 0.4 and less than 0.5 is considered normal in cats and dogs, respectively. A complete urinalysis should always be performed before or along with determination of the urine protein: creatinine ratio because hematuria or pyuria may indicate the presence of nonglomerular proteinuria. If there is evidence of inflammation (e.g., pyuria, bacteriuria), the protein concentration should be measured again after successful treatment of the inflammatory disorder. The urine protein: creatinine ratio cannot be used to differentiate between renal proteinuria and proteinuria associated with lower urinary tract inflammation or hemorrhage. The urine protein:creatinine ratio provides a noninvasive way to follow progression of disease or response to treatment. The variation in urine protein: creatinine observed in dogs with stable proteinuria suggests that the ratio should differ by 80%, especially with lower range proteinuria, in order to conclude that a significant change has occurred. In cats the urine protein: creatinine variation within the reference range suggests that the ratio should differ by 90% to conclude that a significant increase or decrease in proteinuria has occurred. Typically, quantitative measurement of urine protein and creatinine (mg/dl) is performed at reference laboratories and teaching hospitals; however, in-house quantitative urine protein: creatinine measurement has recently become available (Idexx VetTest Chemistry Analyzer, IDEXX Laboratories, Westbrook, Maine), and results appear to correlate well with standard quantitative methodologies.

Antigen capture enzyme-linked immunosorbent assays (ELISA) used to detect low levels of albumin in canine and feline urine (microalbuminuria [MA]) are commercially available (E.R.D.-Screen, Heska Corp., Fort Collins, Colorado). MA is usually defined as a urine albumin concentration between 1.0 and 30 mg/dl. These are concentrations too low to be routinely detected by standard dipstick screening tests. It is interesting to note that the presence of MA has been shown to be an accurate predictor of subsequent renal disease in human beings with both systemic hypertension and diabetes mellitus, and it has also been observed in human beings with systemic diseases that are associated with glomerulopathy. Studies in dogs have shown the prevalence of MA in apparently healthy dogs and Soft Coated Wheaten Terriers genetically predisposed to developing glomerular disease to be 19% and 76%, respectively (Jensen et al., 2001; Vaden et al., 2001). In additional studies, development of MA preceded the development of overt albuminuria in dogs with experimentally induced heartworm disease (Grauer et al., 2002) and in dogs with X-linked hereditary nephropathy (Lees et al., 2002). MA testing should be used when conventional screening tests for proteinuria are negative and increased sensitivity is desired (e.g., screening for early kidney disease in young animals that may have heritable kidney disease or screening for acquired chronic kidney disease in older animals). A positive MA test of suspected renal origin should be pursued with a three-step paradigm of (1) monitoring, (2) investigating, and (3) intervening. The initial step of monitoring involves determining if the albuminuria is persistent or transient. It is important to note that the sensitivity of MA assays makes it likely that some positive results will be caused by benign or physiologic proteinuria. In these cases, follow-up assays should be negative, confirming that the MA was transient. Transient MA is likely to be of little or no consequence. On the other hand, persistent proteinuria/albuminuria of renal origin indicates the presence of kidney disease. Persistent proteinuria/albuminuria can be defined as positive test results on  $\geq 2$  occasions,  $\geq 2$ weeks apart. Because persistent proteinuria/albuminuria can be constant or increase or decrease in magnitude over time, monitoring should use quantitative methods to determine disease trends and/or response to treatment. Quantitative albuminuria assays or the urine protein/creatinine ratio are used to document changes in the magnitude of the albuminuria once its persistence has been confirmed. Changes in the magnitude of proteinuria should always be interpreted in light of the patient's serum creatinine concentration because albuminuria may decrease in association with progressive renal disease as the number of functional nephrons decrease. Decreasing albuminuria in the face of a stable serum creatinine concentration suggests improvement in renal function, whereas decreasing albuminuria in the face of an increasing serum creatinine suggests disease progression.

Once persistent proteinuria has been documented by monitoring, the appropriate response depends on the magnitude of the proteinuria and the health status of the patient (e.g., the presence or absence of azotemia and/or hypertension). The second step of investigation refers to performing new or additional tests to diagnose an underlying/concurrent infectious, inflammatory, or neoplastic disease process or to more completely define the patient's renal disease. Examples of such further investigation may include a complete minimum database, urine culture, measurement of blood pressure, serology for immune-mediated or infectious diseases, radiographs/ultrasound, and renal biopsy.

In cases of persistent proteinuria, where an underlying disorder cannot be identified or treated, the need for treatment of the proteinuria depends on its magnitude and the presence or absence of azotemia. In the absence of azotemia, proteinuria resulting in urine protein: creatinine ratios >1.0 to 3.0 should be treated, whereas continued monitoring and patient investigation should be the primary focus in cases with lesser-magnitude proteinuria. Treatment recommendations in these cases usually include decreased dietary protein intake (early renal failure diets), n-3 fatty acid supplementation (early renal failure diets), low-dose aspirin (0.5 mg/kg q24h administered orally), and angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, benazepril; 0.5 to 1.0 mg/kg q24h administered orally), although it is difficult to separate the effects of individual treatments when they are used in combination. Treatment for persistent proteinuria in azotemic dogs and cats should be initiated when the urine protein:creatinine ratio is ≥0.5 and 0.4, respectively. Treatment recommendations in this case usually include ACE inhibition and renal failure diets.

Urine and serum protein electrophoresis may help in identifying the source of the proteinuria and in establishing a prognosis. For example, proteinuria associated with hemorrhage into the urinary tract has an electrophoretic pattern very similar to that of serum. Early glomerular damage usually results principally in albuminuria; however, as the glomerular disease progresses, an increasing amount of globulin may be lost as well. Marked hypoalbuminemia and increased concentrations of larger-molecular-weight pro-

teins in the serum indicate the presence of severe glomerular proteinuria and the nephrotic syndrome.

# PLASMA AND URINE OSMOLALITY, WATER DEPRIVATION TEST, AND RESPONSE TO EXOGENOUS ANTIDIURETIC HORMONE

Measurement of plasma osmolality may aid in the determination of the primary component of the polydipsia/polyuria (PD/PU) syndrome. Normal plasma osmolality in dogs and cats is 280 to 310 mOsm/kg. Plasma osmolality in animals with primary PD is usually low (275 to 285 mOsm/kg), reflecting the dilutional effect of excessive water consumption. In contrast, animals with a primary PU often have high plasma osmolalities (305 to 315 mOsm/kg) because of their inability to concentrate urine and the resultant dehydration (see Fig. 41-9). However, there can also be considerable overlap in randomly obtained plasma osmolalities between animals with primary polydipsic disorders and those with primary polyuric disorders.

Determination of a urine: plasma osmolality ratio allows a more precise determination of urine concentration than does urine specific gravity alone because specific gravity measures the density of urine rather than the number of particles in solution. For example, moderate-to-marked glucosuria or proteinuria increases urine specific gravity more than the urine osmolality. In response to dehydration, normal dogs and cats should be able to form urine that is five to six times more concentrated than plasma. Plasma and urine osmolality may be determined using either a vapor pressure or freezing point depression osmometer, and measurement is available at a reasonable cost at most veterinary teaching hospitals and reference laboratories.

Water deprivation causes dehydration and plasma hyperosmolality and allows the neurohypophyseal-renal axis to be evaluated. Water deprivation tests are used to differentiate diabetes insipidus from primary PD and should be performed only after other causes of PU and PD have been ruled out on the basis of the findings from physical examination and a minimum database. It should be noted that water deprivation tests are potentially dangerous. They should therefore be performed only under close observation and after water intake has been gradually reduced (see later discussion) because failure to produce concentrated urine (i.e., diabetes insipidus) may result in severe dehydration and potential ischemic renal injury. Increases in plasma osmolality of 1% to 2% above normal levels stimulate the release of antidiuretic hormone (ADH), and normal kidneys should respond to this ADH by producing hypersthenuric urine. The water deprivation test is complete when the animal loses 5% of its body weight as a result of dehydration, becomes azotemic, becomes hyperosmolemic (plasma osmolality ≥320 mOsm/kg), or produces hypersthenuric urine (specific gravity ≥1.030 in dogs or ≥1.035 in cats). It is important to obtain accurate baseline values and ensure that the bladder is emptied each time the urine specific gravity or osmolality is measured so that urine produced between evaluations is not diluted by previously formed urine. Plasma osmolality constitutes a good measure of hydration status during water deprivation, and, in fact, a water deprivation test may not be necessary if it is measured at baseline. The finding of a baseline plasma osmolality of 320 mOsm/kg or greater in a clinically nondehydrated dog or cat with hyposthenuria or isosthenuria indicates a failure of the neurohypophysealrenal axis. Similarly, a water deprivation test should not be performed in an animal that is clinically dehydrated or azotemic and that has hyposthenuria, isosthenuria, or minimally concentrated urine because these conditions already demonstrate a failure of the neurohypophyseal-renal axis. The time it takes to reach the end-point of a water deprivation test is variable; small dogs and cats may dehydrate within several hours, whereas significant dehydration may not occur in large dogs for 36 to 48 hours. Animals that fail to produce hypersthenuric urine in response to water deprivation have either pituitary or nephrogenic diabetes insipidus.

A pharmacologic dose of ADH may be administered to differentiate pituitary diabetes insipidus (lack of ADH) from nephrogenic diabetes insipidus (no response to ADH). Aqueous ADH (3 to 5 U given intramuscularly) is commonly used for diagnostic testing, although synthetic desmopressin acetate nasal spray, given as drops in the conjunctival sac, or an injectable preparation of desmopressin acetate, given subcutaneously (3 to 5 U), may also be used. The ADH should be administered immediately at the end-point of the water deprivation test, before water is made available, in animals that do not respond to water deprivation. It is important that the bladder be empty immediately before the administration of ADH so that the urine produced in response to ADH is not diluted by previously formed urine. Animals with central diabetes insipidus (CDI) usually respond by producing urine that is hypersthenuric or at least ≥1.025 within 1 to 2 hours. The absence of an increase in urine specific gravity in response to both water deprivation and exogenous ADH administration indicates the presence of nephrogenic diabetes insipidus (NDI).

Renal medullary hypertonicity may be lost after prolonged PU (primary or secondary). Therefore medullary washout may develop in animals with primary PD or CDI, making them appear to have NDI. Water intake may be gradually reduced over 10 to 14 days to correct renal medullary washout before the water deprivation test is performed. In addition to gradually limiting the dog's or cat's water intake (10% reduction every other day until the animal is drinking 80 to 90 ml/kg/day), a high-protein diet that is lightly salted (unless the patient is hypertensive) should be fed to the animal to facilitate reestablishment of normal medullary tonicity. Water restriction should be discontinued if the animal becomes overly aggressive in its desire for water or becomes lethargic or weak. The response to water deprivation and, if necessary, the response to exogenous ADH should be evaluated after 10 to 14 days of this gradual water deprivation. The lack of a response to water deprivation and exogenous ADH administration after gradual water reduction suggests that NDI unrelated to medullary washout is the cause of the PD/PU.

# **BLADDER AND URETHRAL FUNCTION**

Several specialized diagnostic tests, including urethral pressure profilometry, cystometry, and uroflowmetry, may help categorize bladder and urethral function in dogs and cats with disorders of micturition. These tests are available at many referral centers. The urethral pressure profile (UPP) assesses the perfusion pressure or minimal distention pressure within the bladder and urethra during the storage phase of micturition. The functional urethral length (the length of the urethra that has a pressure greater than the intravesical pressure) and the functional urethral closure pressure (the greatest urethral pressure minus the intravesical pressure) can be determined on the basis of a UPP. Electromyography may be combined with a UPP to define the portion of urethral resistance contributed to by periurethral striated muscle (external sphincter). The UPP can be used to assess urethral sphincter tone in animals with suspected urethral sphincter incompetence or functional urethral obstruction and urethral spasm. In addition, the UPP can be used to evaluate sphincter response to treatment with α-adrenergic drugs or estrogens. Finally, the UPP should be determined preoperatively to evaluate urethral sphincter function in dogs and cats with ectopic ureters or vaginal strictures because of the increased incidence of sphincter incompetence in animals with these congenital anomalies. A cystometrogram records changes in intravesical pressure during bladder filling and detrusor contraction. It evaluates the detrusor reflex, maximal detrusor contraction pressure, and bladder capacity and compliance in animals with suspected detrusor atony, instability, and decreased capacity or compliance. Uroflowmetry measures urine flow during the voiding phase of micturition and defines the relationship between urine flow and detrusor contraction. The presence of normal, increased, or decreased urethral resistance can be established with uroflowmetry.

# BACTERIAL ANTIBIOTIC SENSITIVITY TESTING

The majority of simple, uncomplicated urinary tract infections in female dogs can be effectively treated with an antibiotic chosen on the basis of urine sediment Gram staining or culture and sensitivity based on the disk-diffusion/Kirby Bauer method. If disk-diffusion sensitivity testing shows that the organism is highly resistant to antibiotics (e.g., susceptible only to aminoglycosides), minimum inhibitory concentration (MIC) sensitivity testing can be helpful because of differences in the serum and urine concentrations of antibiotics. In these cases, in vivo sensitivity may exist even though



TABLE 42-1

Urine Concentration of Selected Antimicrobial Agents in Healthy Dogs with Normal Renal Function

ANTIBIOTIC	DOSAGE*	ROUTE	URINE CONCENTRATION ( $\mu$ g/mL; MEAN $\pm$ STANDARD DEVIATION)
n · · · · · · · · · · · ·	40,000 11/1 01	PO.	294 ± 211
Penicillin G	40,000 U/kg q8h	PO	
Ampicillin	25 mg/kg q8h	PO	309 ± 55
Amoxicillin	11 mg/kg q8h	PO	202 ± 93
Tetracycline	20 mg/kg q8h	PO	138 ± 65
Chloramphenicol	33 mg/kg q8h	PO	124 + 40
Sulfisoxazole	22 mg/kg q8h	PO	1466 ± 832
Cephalexin	30 mg/kg q12h	PO	805 ± 421
Trimethoprim/sulfa	15 mg/kg q12h	PO	55 ± 19
Enrofloxacin	2.5 mg/kg q12h	PO	43 ± 12

<sup>\*</sup> Dosages are the same for cats, except that the dosage or chloramphenicol in cats is 20 mg/kg q8h for 1 week. PO, Orally.

disk-diffusion sensitivity testing has shown in vitro resistance. For example, the MICs of penicillin for staphylococcal organisms, including penicillinase-producing strains, are approximately  $10~\mu g/ml$ . The average urine concentration of ampicillin, when given in standard doses orally, exceeds  $300~\mu$  g/ml, whereas the expected serum concentration is only 1 to  $2~\mu$  g/ml. The general rule of thumb in interpreting MICs is that if the MIC is 25% or less of the expected mean urine concentration (Table 42-1), the organism should be susceptible. However, MIC sensitivity should not be used in animals with pyelonephritis, prostatitis, or bladder infections with a thickened bladder wall because drug concentrations in these tissues will be closer to serum concentrations than to urine concentrations.

# **DIAGNOSTIC IMAGING**

It is relatively difficult to visualize the entire outline of both kidneys on plain abdominal radiographs; the right kidney is usually more difficult to visualize than the left because of its close association with the caudate lobe of the liver. It is even more difficult to visualize the kidneys in thin or emaciated animals because the contrast provided by abdominal fat is lacking. Plain abdominal radiographs are valuable to evaluate kidney number, location, size, shape, and radiographic density (Table 42-2). Kidney size is best estimated by comparing kidney length with the length of adjacent lumbar vertebrae; the kidneys should be approximately equivalent to 2.5 to 3 times the length of the second lumbar vertebra in cats and 2.5 to 3.5 times the length of the second lumbar vertebra in dogs. Canine kidneys are generally bean shaped, whereas feline kidneys are more spherical. The right kidney is approximately one-half length cranial to the left kidney in both cats and dogs, and the kidneys of cats are more movable than those of dogs. Kidneys have a soft tissue or water density throughout and are more dense than the perirenal fat. Any radiopacity within the kidney is abnormal (Fig. 42-1).

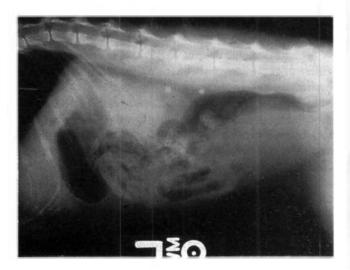


FIG 42-1
Plain film radiographic appearance of bilateral renal calculi in a cat. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

Ultrasonography is used to evaluate renal tissue architecture if kidney abnormalities have been detected by physical examination (e.g., abnormal kidney size or shape), clinicopathologic findings (e.g., azotemia or proteinuria), or survey radiographs (e.g., abnormal kidney size, shape, or opacity or nonvisualization of a kidney). Ultrasonography can provide information about the tissue architecture of the kidneys. Normally, the renal cortex is hypoechoic compared with the spleen, and the renal medulla is hypoechoic compared with the cortex (Fig. 42-2). The renal pelvis and diverticula are relatively hyperechoic. Relatively hypoechoic renal cortices can be observed in patients with acute tubular necrosis, polycystic kidney disease, abscesses, or renal edema associated with acute renal failure. Conversely, relatively hyperechoic renal cortices are associated with chronic kidney disease (CKD), nephrocalcinosis, amyloidosis, feline infectious peritonitis, and calcium oxalate nephrosis secondary to ethylene glycol ingestion. Glomerular and tubulointerstitial disease



**TABLE 42-2** 

## Imaging Procedure and Potential Findings in Cats and Dogs with Urinary Disorders

PROCEDURE	POTENTIAL FINDINGS
	Davidian annua constituta
Plain abdominal radiography	Radiopaque uroliths Increased or decreased kidney size
•	
	Abdominal mass(es) Bladder distention
	Emphysematous cystitis
	Enlarged uterus
	Enlarged prostate
8 I I. I	Lymphadenopathy
Renal ultrasonography	Tissue architecture (diffuse versus focal disease, echodense versus echolucent lesions)
•	Pyelonephritis
	Perirenal fluid, renal cysts, or abscesses
	Hydronephrosis, hydroureter
Excretory urography	Renal parenchymal filling defects
	Renal pelvic dilatation or filling defects
	Hydronephrosis or hydroureter
	Ureteral obstruction
	Ectopic ureter(s)
	Extravasation of contrast material
Contrast-enhanced cystography	Radiolucent uroliths
, - , ,	Intraluminal mass(es)
	Wall thickening
	Urachal remnant
	Extravasation of contrast material
	Enlarged prostate
	Reflux of contrast material into ureters*
Bladder ultrasonography	Intraluminal masses (uroliths, blood clots, tumors, polyps)
3 7 7	Wall thickening
	Prostatic lesions
	Sublumbar lymphadenopathy
Contrast-enhanced urethrography	Intraluminal filling defects
	Extraluminal compression
	Extravasation of contrast material
	Enlarged prostate
	Reflux of contrast material into prostate*
	Kolox of Collinasi fiderial fillo proside

<sup>\*</sup>May be observed in normal dogs.

can show a normal or hyperechoic echotexture depending on chronicity. Renal lymphoma can make the renal cortices appear hypoechoic or hyperechoic (Fig. 42-3). Hydrone-phrosis and hydroureters are easily and noninvasively diagnosed on the basis of ultrasonographic findings (Fig. 42-4). Resistance to renal blood flow (resistive index), which can be calculated with the use of color flow Doppler imaging, is increased in association with several renal diseases.

An intravenous urogram (Box 42-2) can also aid in the evaluation of renal structures, specifically the renal vessels, parenchyma, and pelvis, as well as the ureters (Fig. 42-5). Potential indications for IV urography include kidney abnormalities noted on plain radiographs or ultrasonograms, inability to visualize one or both kidneys on plain radiographs or ultrasonograms, and hematuria of suspected renal origin. In addition, IV urography qualitatively assesses individual kidney excretory function; therefore it should be performed before nephrectomy or nephrotomy if other means of assessing GFR are not available. The utility of IV urography diminishes if azotemia exists, and good renal opacification

becomes more difficult as azotemia increases. IV urography should be avoided in dehydrated animals and in those receiving potentially nephrotoxic drugs.

If the ureters are normal, they cannot be visualized on plain radiographs. Normal ureters appear as radiopaque lines that extend from the kidneys to the trigone region of the bladder on IV urograms (see Fig. 42-5, B). The normal ureteral diameter is 1 to 2 mm, and apparent filling defects are frequently caused by peristaltic contractions that propel urine and contrast material to the bladder. Indications for intravenous urography to evaluate the ureters include suspected obstructive uropathy (Fig. 42-6), trauma (rupture or laceration), calculi, ectopic ureters (Fig. 42-7), neoplasia, and ureterocele.

The size, shape, and position of the urinary bladder can usually be evaluated and any radiopacities detected on plain abdominal radiographs and ultrasonograms (Fig. 42-8). However, retrograde contrast-enhanced radiographic studies are easy to perform and are used to visualize the entire bladder and its relationship to other structures in the

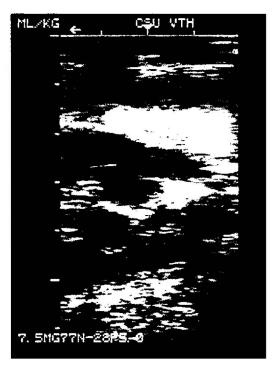


FIG 42-2
Ultrasonographic images of the kidney and spleen in a dog showing the increased echogenicity of the spleen (upper right) compared with the renal cortex. (Courtesy Dr. Robert Wrigley, Colorado State University, Fort Collins, Colo.)

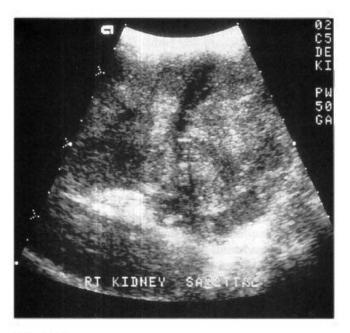


FIG 42-3
Ultrasonographic image of a feline kidney with lymphoma. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)



FIG 42-4
Ultrasonographic image of a hydronephrotic kidney.
(Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)



# BOX 42-2

#### Technique for Intravenous Urography

1. Patient preparation:

No food for 24 hours, water available, free choice One or more enemas at least 2 hours before radiography

Assess hydration status; do not proceed if animal is dehydrated.

- 2. Evaluate survey radiographs for effectiveness of enemas.
- 3. Use sedation only if necessary.
- 4. Infuse contrast solution intravenously via jugular or cephalic vein as bolus injection.

880 mg/kg iodine; dose can be doubled if renal function is poor.

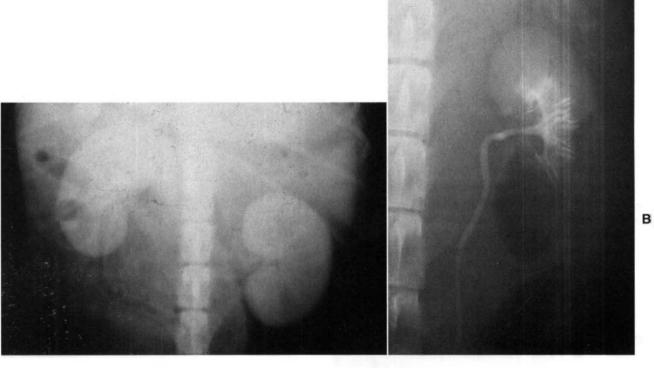
Nonionic iodinated contrast solutions are safest but more expensive.

5. Obtain abdominal radiographs as follows:

Ventrodorsal views at 5 to 20 seconds, 5 minutes, 20 minutes, and 40 minutes after injection

Lateral view at 5 minutes

Oblique views at 3 to 5 minutes to assess ureteral termination in bladder



**FIG 42-5**Radiographic appearance of normal canine kidneys during **(A)** the nephrogram stage of an intravenous pyelogram and **(B)** the pyelogram stage of an intravenous pyelogram.

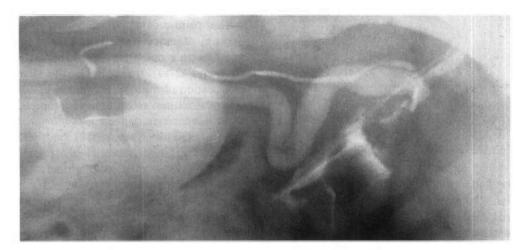


FIG 42-6
Intravenous pyelogram of a dog with a transitional cell carcinoma of the bladder and unilateral hydroureter. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)



FIG 42-7
Intravenous pyelogram of a dog with a unilateral ectopic ureter. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

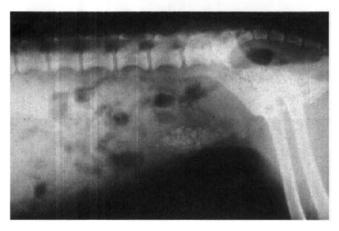


FIG 42-8
Appearance of radiopaque cystouroliths on plain film radiographs of a dog. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

posterior abdomen. Negative (air or carbon dioxide) or positive (iodinated contrast medium) contrast material may be used for contrast-enhanced cystography (Fig. 42-9); however, double-contrast studies (bladder is filled with a positive-contrast medium that is removed and replaced with air or carbon dioxide) provide the best information about the bladder mucosal surface (Fig. 42-10). Abnormalities that may be identified by contrast-enhanced cystography include mucosal and mural lesions, luminal filling defects, urachal remnants, diverticuli, vesicoureteral reflux, extraluminal masses, radiolucent calculi, and bladder tears.

Ultrasonography can also be used to evaluate the urinary bladder, in most cases without the sedation and urinary catheterization required for contrast-enhanced cystography. It is particularly useful for differentiating intraluminal

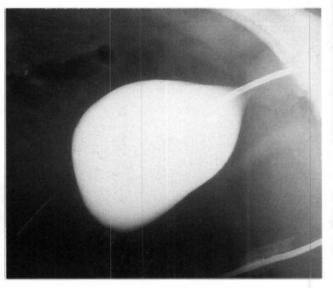


FIG 42-9
Positive contrast–enhanced cystogram in a male dog showing a small urachal remnant. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

masses (e.g., calculi, blood clots, tumors, polyps; Figs. 42-11 and 42-12). The prostate gland and sublumbar lymph nodes are also easily evaluated with ultrasonography. However, it may be less effective than contrast-enhanced cystography in detecting subtle mucosal irregularities, small uroliths, and bladder rupture.

Similar to the ureters, the urethra is not routinely visualized on plain radiographs. Contrast-enhanced urethrography is most frequently performed in male dogs and cats to detect or rule out urethral obstruction or rupture (Figs. 42-13 and 42-14). It may be used to identify the presence and location of mucosal and mural lesions, luminal filling defects, strictures, an extramural compression, and urethral rupture or laceration.

Computed tomography (CT), both plain and with contrast, and magnetic resonance imaging (MRI) are increasingly used for evaluation of urinary tract pathology at teaching hospitals and other referral centers. The three-dimensional anatomical information provided by CT and MRI can be helpful in surgical planning, especially for detection of tumor invasion into adjacent tissues. Intravenous urography with CT is an excellent imaging technique for detection of ectopic ureters, and GFR can be calculated using contrast-enhanced CT images of the kidneys.

#### CYSTOSCOPY

Cystoscopy allows relatively noninvasive visualization and biopsy of the urethral and bladder mucosal surface. In some cases, bladder mucosal lesions can be biopsied or resected and uroliths removed or crushed by means of cystoscopy. Finally, cystoscopy can be used to catheterize the ureters to

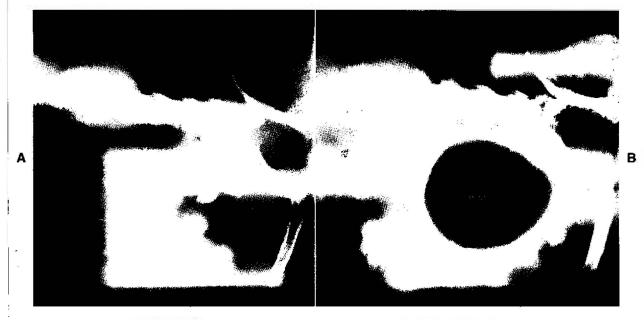


FIG 42-10

Double contrast—enhanced cystograms of a dog showing (A) insufficient distention of the bladder with air, giving an artificial appearance of a thickened bladder wall, and (B) proper distention of the bladder with negative contrast.

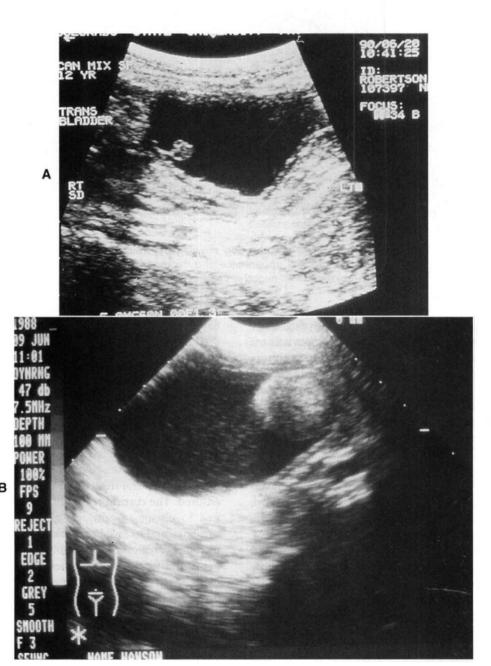
obtain urine samples and perform retrograde pyelography. Cystoscopy is used to evaluate patients with lower urinary tract inflammation, to evaluate potential anatomic abnormalities in animals with recurrent urinary tract infections (e.g., urolithiasis, polyps, urachal remnants) and animals with urine retention or incontinence, to evaluate and obtain a biopsy specimen of bladder or urethral masses, and to differentiate unilateral from bilateral renal hematuria.

# **RENAL BIOPSY**

The biopsy and histopathologic evaluation of renal tissue is a valuable diagnostic and prognostic tool. Renal biopsy should be considered if the diagnosis is in question (e.g., immune complex glomerulonephritis versus amyloidosis in dogs with proteinuria), if treatment may be altered on the basis of results (e.g., confirmation and culture of bacterial pyelonephritis), or if the prognosis may be altered on the basis of results (e.g., evidence of reversible tubular lesions in a dog or cat with acute tubular necrosis). A specific diagnosis is required to implement specific treatment in most animals with renal disease, and a biopsy frequently must be performed for a specific diagnosis to be obtained. In addition, the prognosis for animals with renal disease is most accurate if it is based on three variables: the severity of dysfunction, the response to treatment, and the renal histopathologic findings.

Renal biopsy should be considered only after less invasive tests have been done and the blood clotting ability has been assessed. Absolute or relative contraindications to renal biopsy include a solitary kidney, a coagulopathy, severe systemic hypertension, and renal lesions associated with fluid accumulation (e.g., hydronephrosis, renal cysts and abscesses). In addition, renal biopsy should not be attempted by inexperienced clinicians or in animals that are not adequately restrained.

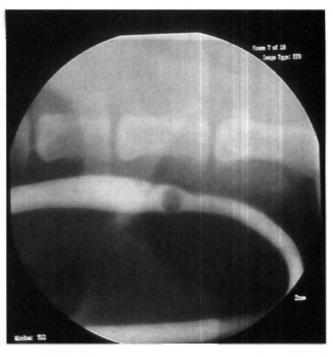
Renal biopsy specimens can be obtained percutaneously using the keyhole technique or under laparoscopic or ultrasonographic guidance. In many cases the best way to obtain a specimen is at laparotomy, when both kidneys can be visualized, because postbiopsy hemorrhage can then be accurately assessed and treated and an adequate biopsy specimen ensured. The cortical region of the kidney should be biopsied to obtain an adequate number of glomeruli in the specimen and to avoid renal nerves and major vessels in the medullary region. Most animals will have microscopic hematuria for 1 to 3 days after the biopsy procedure, and overt hematuria is not uncommon. In a retrospective study by Vaden (2007) of renal biopsies in 283 dogs and 65 cats, complications were reported in 13.4% and 18.5% of dogs and cats, respectively. The most common complication was severe hemorrhage; hydronephrosis and death were uncommon. Dogs that developed complications after renal biopsy were more likely to have been 4 to <7 years of age and >9 years, to weigh ≤5 kg, and to have serum creatinine concentrations >5 mg/dL. The majority of biopsies from both dogs (87.6%) and cats (86.2%) were considered to be of satisfactory quality. Biopsies from dogs were more likely to be of high quality if they were obtained when the patient was under general anesthesia and more likely to contain only renal cortex if they were obtained by surgery. It was concluded that renal biopsy is a relatively safe procedure, with a low frequency of severe complications.



**FIG 42-11**A and **B,** Ultrasonographic images of the bladder of dogs with benign polyps. (A courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)



FIG 42-12
Ultrasonographic image of the bladder of a dog with a transitional cell carcinoma.



**FIG 42-13**Positive contrast–enhanced urethrogram in a dog with an intraluminal urolith. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

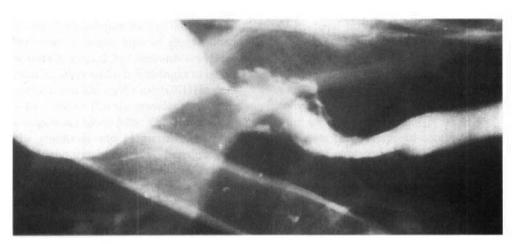


FIG 42-14
Positive contrast-enhanced urethrogram in a dog with an obstructive uropathy associated with prostatic neoplasia.

To prevent artifactual changes, care must be exercised when handling and fixing renal tissue. It is important to consult the histopathology laboratory before performing the biopsy to ensure that appropriate fixatives are used. When possible, immunofluorescent or immunohistochemical techniques and electron microscopy should be used to maximize the information gained from the biopsy specimen. Communication with the laboratory pathologist before biopsy will help determine which fixatives should be used and will maximize the utility of the biopsy sample.

# Suggested Readings

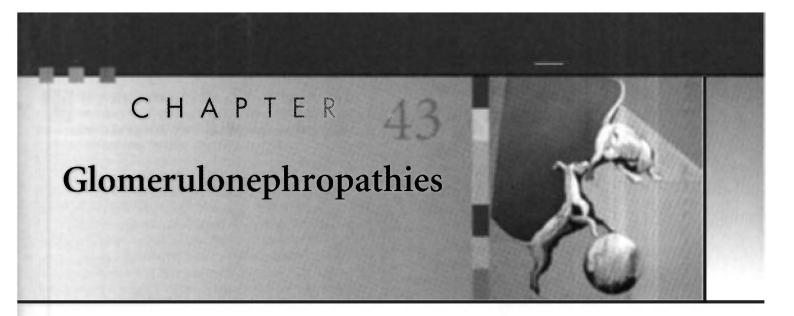
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# CHAPTER OUTLINE

Etiology and Pathophysiology Clinical Features Diagnosis Treatment Monitoring Prognosis

Glomerulonephritis (GN), or inflammation of the glomeruli and tubules, is the most common type of glomerulonephropathy and is usually caused by immune complexes within the glomerular capillary walls. It is thought to be one of the major causes of chronic kidney disease (CKD) in dogs, and several studies have shown that the prevalence of GN in randomly selected dogs is as high as 50%. The deposition of amyloid within the glomeruli and glomerular basement membrane structural abnormalities (e.g., hereditary Xlinked nephropathy of male Samoyeds and Cocker Spaniels) are additional important, although less common, causes of glomerulonephropathy. Loss of plasma proteins, principally albumin, in the urine is the hallmark of glomerulonephropathy. In addition to its diagnostic utility, the magnitude of proteinuria is associated with progression of CKD, and therefore it has become a major focus in the treatment of patients with glomerulopathies.

## **Etiology and Pathophysiology**

Most glomerulonephropathies in dogs and cats are mediated by immunologic mechanisms. Immune complexes present in the glomerular capillary wall are usually responsible for initiating glomerular damage and proteinuria. For example, soluble circulating antigen-antibody complexes may be deposited or trapped in the glomeruli (Fig. 43-1). In contrast to the glomerular deposition of preformed complexes, immune complexes may also form *in situ* in the glomerular capillary wall (see Fig. 43-1). This occurs when circulating antibodies react with endogenous glomerular antigens or "planted," nonglomerular antigens in the glomerular capil-

lary wall. Nonglomerular antigens may localize in the glomerular capillary wall as a result of an electrical charge interaction or a biochemical affinity with the glomerular capillary wall. Immune complexes have been shown to form *in situ* in dogs with glomerulonephritis associated with dirofilariasis.

Although antibodies directed against intrinsic glomerular basement membrane material have not been found in dogs and cats with naturally occurring glomerulonephritis, several infectious and inflammatory diseases have been associated with immune-mediated glomerular disease (Box 43-1). In many cases, however, the antigen source or underlying disease is not identified; in such cases, the glomerular disease is referred to as *idiopathic*. It is not difficult to identify endogenous immunoglobulin or complement within glomeruli using various immunologic techniques, but the antigens associated with the immune complex within glomerular tissue are rarely identified.

Despite the widespread acceptance of the term *GN*, in most cases glomerular lesions associated with the presence of immune complexes do not have classic evidence of neutrophilic inflammation. In very simplistic terms, the histopathologic changes observed in the glomerulus usually include one or more of the following: cellular proliferation, mesangial matrix expansion, and capillary wall thickening. Additional histopathologic subclassification of glomerular lesions associated with immune complexes that use immunohistochemical and ultrastructural studies will be necessary to improve the ability to effectively treat and accurately prognosticate this disease process.

The glomerulus provides a unique environment for injurious immune complexes to stimulate production of bioactive mediators such as proinflammatory cytokines, vasoactive substances, growth factors, and extracellular matrix proteins and proteases that can contribute to the injury (see Fig. 43-1). These substances may be produced by endogenous glomerular cells or by platelets, macrophages, and neutrophils that are attracted to the immune-mediated lesion. For example, activation of the renin-angiotensin-aldosterone system (RAAS) can have hemodynamic and inflammatory/ fibrotic effects on the kidney. The main hemodynamic effect

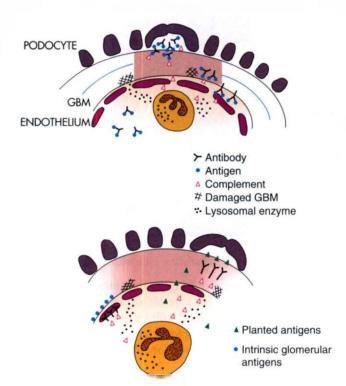


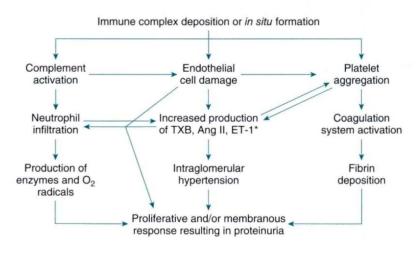
FIG 43-1

The two major types of immunologically mediated glomerular injury. Circulating soluble immune complexes have become trapped in the glomerular filter and have fixed complement. Chemotactic complement components have attracted neutrophils to the area. The release of oxygen free radicals and lysosomal enzymes from neutrophils has resulted in damage to the glomerulus (top). Damage may also result from the attachment of antibodies directed against fixed intrinsic glomerular antigens (bottom, left). Finally, damage may result from the attachment of antibodies directed against planted nonglomerular antigens (bottom, right). GBM, Glomerular basement membrane; PMN, polymorphonuclear leukocyte. (From Chew DJ et al: Manual of small animal nephrology and urology, London, 1986, Churchill Livingstone.)

is vasoconstriction of the efferent glomerular arteriole, resulting in intraglomerular hypertension. This increased hydrostatic pressure within the glomerular capillaries helps drive plasma albumin through the injured glomerular capillary wall. Angiotensin and aldosterone are also proinflammatory and can stimulate glomerular cell proliferation and fibrosis. Aldosterone also stimulates release of plasminogen activator inhibitor 1 (PAI-1), a powerful inhibitor of fibrinolysis that perpetuates glomerular thrombosis (see next paragraph).

In addition to the RAAS, several factors, including activation of the complement system, platelet aggregation, activation of the coagulation system, and fibrin deposition, also contribute to glomerular damage. Platelet activation and aggregation occur secondarily to endothelial damage or antigen-antibody interaction. Platelets, in turn, exacerbate glomerular damage by release of vasoactive and inflammatory substances and by activation of the coagulation cascade. Platelets are also capable of releasing growth-stimulating factors that promote proliferation of vascular endothelial cells. The glomerulus responds to this injury by cellular proliferation, thickening of the glomerular basement membrane, and, if the injury persists, hyalinization and sclerosis (Fig. 43-2). In those cases when identification and correction of an underlying disease process is not possible, treatment is focused on decreasing this glomerular response to the immune complexes (e.g., angiotensin and platelet antagonists).

Once a glomerulus has been irreversibly damaged by GN, the entire nephron becomes nonfunctional. Fibrosis and scarring of irreversibly damaged nephrons may resemble primary interstitial inflammation. In fact, for many years renal interstitial inflammation, or "chronic interstitial nephritis," was thought to be the primary lesion that caused CKD in dogs. As more and more nephrons become involved, glomerular filtration *in toto* decreases. Remaining viable nephrons compensate for the decrease in nephron numbers with increased individual glomerular filtration rates (Fig. 43-3). This "hyperfiltration," coupled with systemic



\*TXB, Thromboxane; Ang II, angiotensin II; ET-1, endothelin-1.

FIG 43-2
Glomerular response to the presence of immune complexes.



BOX 43-1

## Diseases Associated with Glomerulonephritis in Dogs and Cats

#### Dogs Infectious

Canine adenovirus I Bacterial endocarditis

Brucellosis Dirofilariasis Ehrlichiosis

Leishmaniasis Pyometra

Borelliosis Chronic bacterial infections (gingivitis, pyoderma)

Rocky Mountain spotted fever

Trypanosomiasis Septicemia Helicobacter?

# Neoplasia Inflammatory

**Pancreatitis** 

Systemic lupus erythematosus Other immune-mediated diseases

Prostatitis Hepatitis

Inflammatory bowel disease

#### **Various Types**

Hyperadrenocorticism and long-term, high-dose corticosteroids? Idiopathic

Familial

Nonimmunologic-hyperfiltration?

Diabetes mellitus

#### Cats Infectious

Feline leukemia virus
Feline immunodeficiency virus
Feline infectious peritonitis
Mycoplasma polyarthritis
Chronic bacterial infections

## Neoplasia Inflammatory

**Pancreatitis** 

Systemic lupus erythematosus Other immune-mediated diseases

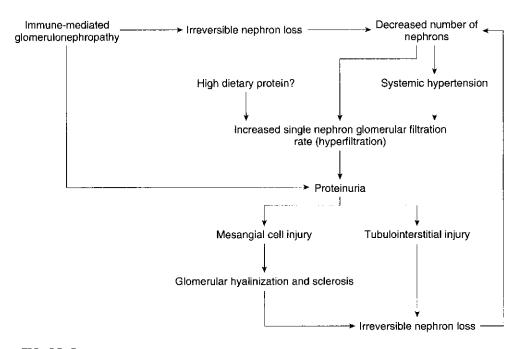
Chronic skin disease

#### Various Types

Idiopathic Familial

Nonimmunologic -- hyperfiltration?

Diabetes mellitus



**FIG 43-3**Proposed pathogenesis of progressive loss of nephrons secondary to a primary glomerulonephropathy.

hypertension if present, may further contribute to glomerular hyalinization and sclerosis. Although it has not been documented in dogs with naturally occurring GN, hyperfiltration and proteinuria in remnant nephrons may result in progressive nephron loss, independent of the primary disease process.

Although glomerular amyloidosis is less common than GN, it is a progressive disease that also frequently leads to CKD. It is characterized by the extracellular deposition of nonbranching fibrillar proteins that stack into a specific  $\beta$ -pleated sheet conformation and exhibit green birefringence under polarized light when stained with Congo red (Fig. 43-4). Amyloidosis in dogs and cats is the reactive systemic form, in which amyloid may be deposited in several organs besides the kidneys. Reactive systemic amyloid deposits contain amyloid protein AA, which is an amino-terminal fragment

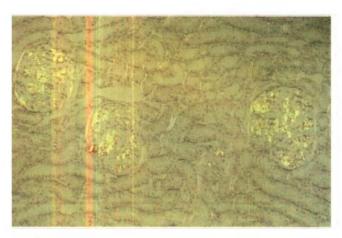


FIG 43-4
Typical appearance of glomerular amyloid (green birefringence) when renal tissue is stained with Congo red and viewed under polarized light.

of the acute-phase reactant protein, serum amyloid A protein (SAA), and is produced by hepatocytes in response to tissue injury. Cytokines (e.g., interleukins, tumor necrosis factor) released from macrophages after tissue injury stimulate hepatocytes to produce SAA. Amyloidosis is usually associated with an underlying inflammatory or neoplastic process; however, no predisposing factors can be identified in many dogs and cats with amyloidosis. Amyloidosis has been associated with cyclic neutropenia and with ciliary dyskinesia and recurrent respiratory tract infections in dogs. Renal amyloidosis is a familial disease in the Abyssinian cat; it results in medullary (not glomerular) amyloid deposition as a part of systemic amyloidosis. A similar form of suspected familial medullary amyloidosis resulting in renal failure has been observed in Chinese Shar-Pei dogs. Intermittent fever that occurs in association with tibiotarsal joint swelling and that resolves regardless of treatment is often observed in these dogs. The staining characteristics of the amyloid in Chinese Shar-Peis indicate that the amyloid is an inflammatory type. This amyloidosis syndrome in Chinese Shar-Peis is similar to that observed in people with familial Mediterranean fever. The medullary deposition of amyloid in Abyssinian cats and Chinese Shar-Pei dogs makes proteinuria uncommon; renal failure, however, is a common sequela.

#### **Clinical Features**

There may be no clinical signs associated with low level proteinuria; alternatively, if signs are present they are usually mild and nonspecific (e.g., weight loss and lethargy). If proteinuria is severe and results in serum albumin concentration <1.5 to 1.0 mg/dl, edema and/or ascites may occur (Table 43-1). If the glomerular disease process causes loss of more than three quarters of the nephrons, clinical signs consistent with advanced stage CKD may be present (e.g., polydipsia-polyuria, anorexia, nausea, vomiting, weight



**TABLE 43-1** 

Signs Associated with Different Manifestations of Glomerular Disease

MANIFESTATION	CLINICAL SIGNS	CLINICOPATHOLOGIC FINDINGS
Mild-to-moderate proteinuria*	Lethargy, mild weight loss, decreased muscle mass	Serum albumin 1.5-3.0 g/dl
Marked proteinuria (>3.5 g/day)	Severe muscle wasting, weight gain may occur, however, as result of edema or ascites	Serum albumin <1.5 g/dl, hypercholesterolemia
Renal failure	Depression, anorexia, nausea, vomiting, weight loss, polyuria- polydipsia	Azotemia, isosthenuria or minimally concentrated urine, hyperphosphatemia, nonregenerative anemia
Pulmonary thromboembolism	Acute dyspnea or severe panting	Hypoxemia; normal or low Pco <sub>2</sub> ; fibrinogen >300 mg/dl; antithrombin <70% of normal
Retinal hemorrhage and/or detachment	Acute blindness	Systolic blood pressure >180 mm Hg

<sup>\*</sup>Microalbuminuria, as discussed in Chapter 42, may precede proteinuria and therefore be an early diagnostic tool. PCO<sub>2</sub>, Partial pressure of carbon dioxide.

loss). Occasionally, clinical signs associated with an underlying infectious, inflammatory, or neoplastic disease may be the reason owners seek veterinary care. Rarely, dogs may be presented with acute dyspnea or severe panting caused by a pulmonary thromboembolism or may have signs associated with thromboembolism elsewhere (e.g., lameness from aortic thromboembolism).

Persistent proteinuria may lead to clinical signs of nephrotic syndrome, which is usually defined as a combination of proteinuria, hypoalbuminemia, ascites or edema, and hypercholesterolemia. Decreased plasma oncotic pressure and hyperaldosteronism activity causing sodium retention are thought to be the primary cause of ascites and edema. It has also been hypothesized that intrarenal mechanisms, independent of aldosterone, may contribute to sodium retention. The hypercholesterolemia associated with the nephrotic syndrome probably occurs because of a combination of decreased catabolism of proteins and lipoproteins and increased hepatic synthesis of proteins and lipoproteins. This results in the accumulation of large-molecular-weight, cholesterol-rich lipoproteins, which are not as easily lost through the damaged capillary wall as are the smallermolecular-weight proteins, such as albumin.

In addition to the previously mentioned clinical signs, systemic hypertension and hypercoagulability are frequent complications in dogs with nephrotic syndrome. A combination of activation of the RAAS and decreased renal production of vasodilators, coupled with increased responsiveness to normal vasopressor mechanisms, are likely involved in the pathogenesis of the systemic hypertension. Systemic hypertension has been commonly associated with immunemediated GN, glomerulosclerosis, and amyloidosis, and in one study, 84% of dogs with glomerular disease were found to be hypertensive. Retinal changes, including hemorrhage, detachment, and papilledema, can be consequences of systemic hypertension; occasionally, blindness may be the presenting sign in hypertensive dogs. In most cases, the systemic hypertension is thought to occur secondary to the kidney disease rather than being a primary entitiy that causes the kidney disease. Systemic hypertension can be transmitted into the glomerular capillaries, especially as autoregulation fails, resulting in intraglomerular hypertension. This increased hydrostatic pressure within glomerular capillaries can exacerbate loss of plasma proteins across the already abnormal capillary wall or sufficiently damage the wall to induce nascent glomerular protein loss. Blood pressure measurement should be part of the evaluation and management of dogs with glomerular disease because it is likely that control of systemic hypertension may slow the progression of glomerular disease.

Hypercoagulability and thromboembolism associated with the nephrotic syndrome occur secondarily to several abnormalities in hemostasis. In addition to mild thrombocytosis, a hypoalbuminemia-related platelet hypersensitivity increases platelet adhesion and aggregation proportionally to the magnitude of hypoalbuminemia. Loss of antithrombin (AT) in urine also contributes to hypercoagulability.

Antithrombin works in concert with heparin to inhibit serine proteases (clotting factors II, IX, X, XI, and XII) and normally plays a vital role in modulating thrombin and fibrin production. Finally, impaired fibrinolysis caused by aldosterone-induced production of PAI-1 further enhances blood clotting. The pulmonary arterial system is the most common location for a thromboembolic disease in dogs with glomerular lesions. Dogs with pulmonary thromboembolism are usually dyspneic and hypoxemic and have minimal pulmonary parenchymal radiographic abnormalities. Treatment of pulmonary thromboembolism is difficult, often expensive, and frequently unrewarding; therefore early prophylactic treatment to prevent thrombus formation is important.

There is increasing suspicion that proteinuria may cause glomerular and tubulointerstitial damage that can lead to progressive nephron loss in dogs and cats. Plasma proteins that have crossed the glomerular capillary wall can accumulate within the glomerular tuft and stimulate mesangial cell proliferation and increased production of mesangial matrix. In addition, excessive amounts of protein in the glomerular filtrate can damage tubular epithelial cells and lead to interstitial inflammation, fibrosis, and cell death. Mechanisms for the tubulointerstitial lesions associated with proteinuria include tubular cell lysosomal damage/rupture, peroxidative and immune-mediated damage, increased production of growth factors, cytokines and vasoactive agents, and transdifferentiation of tubular cells to myoepithelial cells that can produce collagen.

In dogs with naturally occurring CKD, proteinuria resulting in a urine protein: creatinine ratio ≥1.0 was associated with a threefold greater risk of developing uremic crises and death compared with dogs with urine protein: creatinine ratio < 1.0. The relative risk of adverse outcome was approximately 1.5 times higher for every 1 unit increase in urine protein: creatinine ratio. In addition, dogs with urine protein:creatinine ratio ≥1.0 had a decrease in renal function that was greater in magnitude than that observed in dogs with urine protein: creatinine ratio <1.0. In cats with naturally occurring CKD, proteinuria appears to be very highly related to survival. The hazard ratios (95% confidence intervals) for death or euthanasia were 2.9 and 4.0 for urine protein: creatinine ratio 0.2 to 0.4 and >0.4, respectively, compared with the baseline group with a urine protein: creatinine ratio <0.2. On the basis of this evidence, it is possible that proteinuria is not only a marker of CKD in the dog and cat but also a mediator of progressive renal injury. Attenuation of proteinuria should be a major treatment objective in dogs and cats with CKD.

# Diagnosis

Persistent, severe proteinuria with a normal urine sediment (hyaline casts may be observed) is the hallmark clinicopathologic sign of glomerulonephropathies. The urine protein: creatinine ratio is used to quantify the magnitude of the urine protein loss. Microalbuminuria may precede overt proteinuria in many cases (see the section on proteinuria in Chapter 42). Protein-losing nephropathies are definitively diagnosed on the basis of renal cortical histopathologic findings. (See sections on proteinuria and renal biopsy in Chapters 41 and 42.)

#### **Treatment**

Inasmuch as immune complexes usually initiate GN, primary treatment objectives include (1) identification and elimination of causative/associated antigens and (2) reduction of the glomerular response to the immune complexes.

Elimination of the source of antigenic stimulation is the treatment of choice for GN. For example, proteinuria associated with dirofilariasis in dogs often improves or resolves after successful treatment of parasitic infection. Unfortunately, elimination of the antigen source often is not possible because the antigen source or underlying disease may not be identified or may be impossible to eliminate (e.g., neoplasia). In a retrospective study by Cook (1996) of 106 dogs with GN, 43% had no identifiable concurrent disease or disorder and 19% had neoplasia. Infection, polyarthritis, hepatitis, hyperadrenocorticism, and immune-mediated hemolytic anemia are additional commonly identified concurrent medical problems (Box 43-2).

Immunosuppressive drugs have been recommended in dogs with GN, but despite these recommendations, there has been only one controlled clinical trial in veterinary medicine assessing the effects of immunosuppressive treatment. In this



BOX 43-2

Treatment Guidelines for Dogs and Cats with Glomerulonephritis

- 1. Identify and eliminate any underlying diseases
- Immunosuppressive treatment (usually not recommended for dogs)
  - a. Cyclophosphamide, 50 mg/m² PO q48h (dogs) or 200 to 300 mg/m² PO q3wk (cats) or
  - b. Azathioprine,  $50 \text{ mg/m}^2 \text{ PO } \text{ q}24\text{h} \times 7 \text{ days, then } \text{q}48\text{h} \text{ (dogs only) or}$
  - c. Cyclosporine A, 15 mg/kg PO q24h (dogs only)
  - d. Prednisone, 1.0 to 2.0 mg/kg PO q12-24h (cats only)
- Antiinflammatory-hypercoagulability treatment: aspirin, 0.5 to 5.0 mg/kg PO q12h (dogs); 0.5 to 5.0 mg/kg PO q48h (cats)
- Supportive care
  - Dietary: sodium restriction, high-quality-low-quantity protein
  - b. Hypertension: dietary sodium reduction; ACEIs (e.g., enalapril, 0.5 mg/kg PO q12-24h, or benazepril, 0.25 to 0.5 mg/kg PO q24h; ACEIs often have antiproteinuric effects as well) and/or calcium channel blockers
  - Edema and ascites: dietary sodium restriction; furosemide, 2.2 mg/kg PO q8-24h, if necessary

study by Vaden (1995) cyclosporine treatment was found to be of no benefit in reducing proteinuria associated with GN in dogs. The association between hyperadrenocorticism or long-term exogenous corticosteroid administration and GN and thromboembolism in the dog, as well as the lack of consistent therapeutic response to corticosteroids, raises questions about use of these drugs in dogs with GN. In a retrospective study of dogs with naturally occurring GN, treatment with corticosteroids appeared to be detrimental, leading to azotemia and worsening of proteinuria. Similarly, prednisone increased the urine protein: creatinine level from 1.5 to 5.6 in carrier female dogs with X-linked hereditary nephropathy. Consequently, routine use of corticosteroids to treat GN in dogs is not recommended. Treatment with corticosteroids may be indicated, however, if the underlying disease process is known to be steroid responsive (e.g., systemic lupus erythematosus). It is likely that there are specific subtypes of canine immune complex GN (e.g., minimal change GN) that are steroid responsive if they are appropriately identified and treated.

If an underlying or concurrent disease process cannot be identified and treated, or if immunosuppressive treatment is deemed inappropriate, treatment may be aimed at decreasing the glomerular response to the presence of immune complexes. Platelets appear to play an important role in the glomerular response to immune complexes, and therefore aspirin treatment is often recommended. Appropriate dosage is probably important if nonspecific cyclooxygenase inhibitors, such as aspirin, are used to decrease glomerular inflammation and platelet aggregation. An extremely low dosage of aspirin (0.5 mg/kg administered orally once a day) may selectively inhibit platelet cyclooxygenase without preventing the beneficial effects of prostacyclin formation (e.g., vasodilation, inhibition of platelet aggregation). Low-dose aspirin is easily administered on an outpatient basis and does not require extensive monitoring. Because fibrin accumulation within the glomerulus is a frequent and irreversible consequence of GN and thromboembolic disorders can complicate the management of protein-losing nephropathies, antiplatelet/anticoagulant treatment with aspirin may serve several purposes.

Treatment with angiotensin-converting enzyme inhibitors (ACEIs) can reduce proteinuria and slow disease progression. In dogs with unilateral nephrectomy and experimentally induced diabetes mellitus, ACEI administration reduced glomerular transcapillary hydraulic pressure and glomerular cell hypertrophy as well as proteinuria. In another study by Grodecki (1997) ACEI treatment of Samoyed dogs with Xlinked hereditary nephritis decreased proteinuria, improved renal excretory function, decreased glomerular basement membrane splitting, and prolonged survival compared with control dogs. A double-blind, multicenter, prospective clinical trial assessed the effects of enalapril (EN) versus standard care in dogs with naturally occurring, idiopathic GN. The enalapril treatment group had decreased proteinuria, systolic blood pressure, and stable renal function compared with the placebo-treated group. In prospective randomized, controlled clinical trials (King, 2006; Mizutani, 2006) in cats with spontaneous CKD, benazepril has been shown to reduce proteinuria, delay CKD progression, and extend survival time.

Treatment with ACEI probably decreases proteinuria and preserves renal function associated with glomerular disease by several mechanisms. In dogs administration of lisinopril decreases efferent glomerular arteriolar resistance, which results in decreased glomerular transcapillary hydraulic pressure and decreased proteinuria. In rats administration of EN prevents the loss of glomerular heparan sulfate that can occur with glomerular disease. Administration of ACEI also is thought to attenuate proteinuria by decreasing the size of glomerular capillary endothelial cell pores in people. In addition, the antiproteinuric and renal protective effects of ACEI in people may be, in part, associated with improved lipoprotein metabolism. Decreased production of angiotensin and aldosterone may also result in decreased renal fibrosis. Finally, administration of ACEI in dogs slows glomerular mesangial cell growth and proliferation that can alter the permeability of the glomerular capillary wall and lead to glomerulosclerosis.

Supportive therapy is important in the management of dogs with GN and should be aimed at alleviating systemic hypertension, decreasing edema/ascites, and reducing the risk of thromboembolism. ACEIs are recommended as the first line of treatment for proteinuric, hypertensive dogs. In those cases wherein systemic hypertension is refractory to ACEI treatment, a calcium channel blocker should be added to the antihypertensive regimen. Although similar studies have not been performed in dogs or cats, in people the combination of ACEI and an aldosterone receptor antagonist (e.g., spironolactone) have had additive effects in reducing proteinuria and renal disease progression.

Cage rest and restriction of dietary sodium should be the primary treatment considerations for patients with edema and/or ascites. Paracentesis and diuretics should be reserved for those dogs with respiratory distress or abdominal discomfort. Overzealous use of diuretics may cause dehydration and acute renal decompensation. Plasma transfusions will provide only temporary benefit in terms of increasing oncotic pressure resulting from the addition of albumin. In the past, dietary protein supplementation was recommended to offset the effects of proteinuria and reduce edema and ascites; however, recent studies in proteinuric heterozygous female dogs with X-linked nephropathy suggest that reduced dietary protein is associated with reduced proteinuria. N-3 fatty acid supplementation may also be beneficial; in dogs with surgically reduced remnant kidneys, dietary supplementation with fish oil reduced proteinuria, intraglomerular pressures, and glomerular lesion and maintained the glomerular filtration rate.

Similar to the treatment of GN, the primary treatment for amyloidosis, if possible, should be the identification and treatment of any underlying inflammatory process. Dimethylsulfoxide (DMSO) has been shown to dissolve amyloid fibrils *in vitro* and *in vivo* in mice. It has been hypothesized

that DMSO has a similar amyloid-dissolving effect in domestic animals. The antiinflammatory effects of DMSO may also serve to decrease production of the acute-phase reactant SAA and the inflammation associated with an underlying disease. Decreased urinary protein excretion was observed in one dog with amyloidosis treated with DMSO; however, the effects of DMSO were difficult to determine because two potential underlying causes (interdigital pyoderma and a Sertoli cell tumor) were eliminated before the DMSO treatment. The dosage of DMSO used in that dog was 80 mg/kg administered subcutaneously three times per week; the treatment was continued for more than a year without apparent adverse effects. Other studies assessing the effects of DMSO in dogs with amyloidosis, however, have shown the treatment to be ineffective.

Colchicine is another drug that is frequently mentioned for the treatment of amyloidosis. It prevents the production of SAA by hepatocytes and has been shown to prevent amyloidosis in humans and mice if used early in the disease. Although colchicine has been recommended to prevent medullary amyloidosis in Chinese Shar-Pei dogs with fever and tibiotarsal joint swelling, no controlled studies of its use in this setting have been performed. The dosage of colchicine that has been recommended for the prophylactic treatment of amyloidosis is 0.025 mg/kg given orally q24h. Increasing the dose to 0.025 mg/kg, given orally q12h, may be considered if the animal tolerates the initial dose well for 2 weeks. However, because adverse effects of colchicine include bone marrow toxicity, the patient should be monitored closely with periodic complete blood counts.

# Monitoring

It is important to monitor the urine protein: creatinine ratio after initiating treatment. Immunosuppressive treatment could alter the ratio of antigen to antibody, thus exacerbating the glomerular lesions and the proteinuria (i.e., a decrease in antibody formation leading to a mild excess of antigen or equal amounts of antigen and antibody in the immune complexes), in which case treatment should be altered or discontinued. In addition, corticosteroids can induce proteinuria owing to a number of mechanisms, so an increase in the urine protein: creatinine ratio can be iatrogenic, not necessarily a result of the progression of the disease. Lack of response to ACEI treatment may suggest the need for increasing the dosage or adding one or more drugs.

In addition, blood pressure and serum creatinine and urea nitrogen concentrations should be monitored in animals with GN. In cases in which the glomerular filtration rate depends on sodium retention and volume expansion, treatment with ACEIs can be associated with a decrease in renal excretory function. Finally, although proteinuria then occurs before the onset of azotemia, GN can lead to CKD. With the development of CKD, the glomerular filtration rate decreases and the proteinuria therefore usually also decreases. Management guidelines for CKD are presented in Chapter 44.

## **Prognosis**

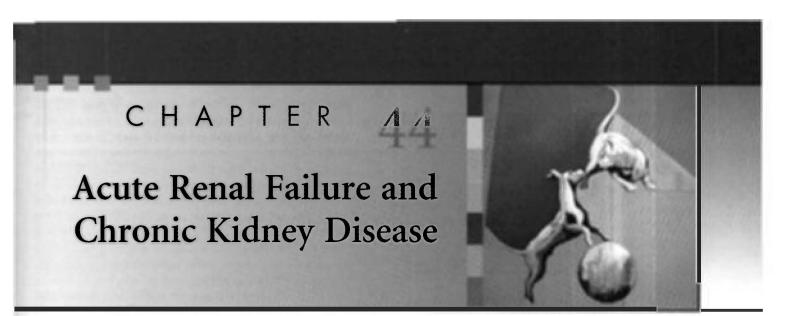
The prognosis for dogs with GN is variable and is best based on consideration of the following factors: severity of dysfunction (i.e., the magnitude of the proteinuria and the presence or absence of azotemia), the response to therapy, and the assessment of renal histopathology. Clinical experience suggests that the disease is progressive in many cases, but decreases in the urine protein: creatinine ratio and increases in albumin and AT concentration can occur in dogs with immune-mediated GN treated with diet, ACEIs, and low-dose aspirin. In selected cases, immunosuppressive treatment with corticosteroids and azathioprine may be of benefit.

Inasmuch as glomerular amyloid deposition results in severe proteinuria, with its attendant effects, the disease is relentlessly progressive, often resulting in CKD and uremia; and given that no specific treatment has proved to be effective, the prognosis for animals with renal amyloidosis is guarded to poor.

# Suggested Readings

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# CHAPTER OUTLINE

# **ACUTE RENAL FAILURE**

Etiology and Pathogenesis Clinical Features and Diagnosis Risk Factors for Acute Renal Damage/Failure Monitoring Patients at Risk for Acute Renal Damage/ Failure

Treatment of Established Acute Renal Failure CHRONIC KIDNEY DISEASE

Etiology and Pathogenesis Clinical Features and Diagnosis Staging Chronic Kidney Disease Further Diagnostics and Treatment

Renal failure occurs when approximately three fourths of the nephrons of both kidneys cease to function. Acute renal failure (ARF) results from an abrupt decline in renal function and is usually caused by an ischemic or toxic insult to the kidneys, although leptospirosis is reemerging as an important infectious cause of ARF. Ischemic or toxicantinduced injury usually results in damage to the metabolically active epithelial cells of the proximal tubules and thick ascending loop of Henle, causing impaired regulation of water and solute balance. Nephrotoxicants interfere with essential tubular cell functions and cause cellular injury, swelling, and death. Renal ischemia causes cellular hypoxia and substrate insufficiency, which leads to the depletion of adenosine triphosphate (ATP), cellular swelling, and death. Vasoconstriction secondary to toxic or ischemic tubular epithelial injury further decreases glomerular filtration. It is important to note, however, that tubular lesions and dysfunction caused by toxic and ischemic insults may be reversible. In contrast, the nephron damage associated with chronic kidney disease (CKD) is usually irreversible. Regardless of whether the underlying disease primarily affects the glomeruli, tubules, interstitium, or renal vasculature, irreversible damage to any portion of the nephron renders the entire nephron nonfunctional. Irreversibly damaged nephrons are replaced by fibrous connective tissue; therefore a specific cause is rarely determined once end-stage kidney damage is present. CKD occurs over a period of weeks, months, or years and is a leading cause of death in dogs and cats. Once advanced stage CKD has occurred, improving renal function is usually not possible. The goal of CKD treatment is three-fold: (1) to identify and correct the primary disease process, (2) to monitor and slow disease progression, and (3) to alleviate patient clinical signs.

Many different and sometimes confusing terms are used to describe renal function and its deterioration (Fig. 44-1):

- *Renal disease* implies the existence of renal lesions; it does not qualify the cause, severity, or distribution of the lesions or the degree of renal function.
- *CKD* refers to a loss of nephrons associated with prolonged (usually longer than 2 months) and often progressive disease process.
- Renal reserve may be thought of as the percentage of "extra" nephrons available (i.e., those not necessary to maintain normal renal function). Although it probably varies from animal to animal, it is greater than 50% in normal cats and dogs.
- Renal insufficiency begins when the renal reserve is lost.
   Animals with renal insufficiency outwardly appear normal but have a reduced capacity to compensate for stresses such as infection or dehydration and have reduced ability to concentrate urine.
- Azotemia is the increased concentration of urea nitrogen, creatinine, and other nonproteinaceous nitrogenous waste products in the blood.
- Renal azotemia denotes azotemia caused by renal parenchymal lesions.
- Renal failure is a state of decreased renal function that allows persistent abnormalities (azotemia and inability to concentrate urine) to exist; it refers to a level of organ function rather than a specific disease entity.
- Uremia is the presence of all urine constituents in the blood. It may occur secondary to renal failure or postrenal disorders, including urethral obstruction and urinary bladder rupture.

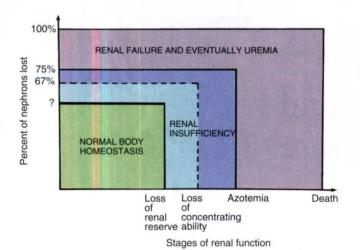


FIG 44-1
The stages of renal function. (From Grauer G et al: Chronic renal failure in the dog, Compend Contin Educ Pract Vet 3:1009, 1981.)



BOX 44-

Factors that May Predispose the Kidney to Ischemia and Toxicant-Induced Injury

The kidneys receive 20% of cardiac output; the cortex receives 90% of the renal blood flow.

The glomerular capillaries have a large surface area.

Proximal tubule and thick ascending loop of Henle cells have a high metabolic rate and are susceptible to hypoxia and nutrient deficiency.

Tubular secretion and resorption may concentrate toxicants within cells.

A countercurrent multiplier system may concentrate toxicants within the medulla.

Xenobiotic metabolism within the kidney may generate toxic metabolites (e.g., metabolism of ethylene glycol).

The *uremic syndrome* is a constellation of clinical signs (e.g., gastroenteritis, acidosis, pneumonitis, osteodystrophy, and encephalopathy) that occur secondary to uremia.

#### **ACUTE RENAL FAILURE**

## **Etiology and Pathogenesis**

The kidneys are highly susceptible to the effects of ischemia and toxicants because of their unique anatomic and physiologic features (Box 44-1). For example, the large renal blood flow (approximately 20% of the cardiac output) results in the increased delivery of blood-borne toxicants to the kidney, as compared with that to other organs. The renal cortex is especially susceptible to toxicants because it receives 90% of the renal blood flow and contains the large endothelial

surface area of the glomerular capillaries. Within the renal cortex, the epithelial cells of the proximal tubule and thick ascending loop of Henle are most frequently affected by ischemia and toxicant-induced injury because of their transport functions and high metabolic rates. Toxicants disrupt the metabolic pathways that generate ATP, and ischemia can rapidly deplete cellular ATP stores. With the resulting loss of energy, the sodium-potassium pump (Na/K) fails, leading to cell swelling and death. By resorbing water and electrolytes from the glomerular filtrate, tubular epithelial cells may be exposed to increasingly higher concentrations of toxicants. Toxicants that are either secreted or resorbed by tubular epithelial cells (e.g., gentamicin) may accumulate in high concentrations within these cells. Similarly, the countercurrent multiplier system may concentrate toxicants in the medulla. Finally, the kidneys also play a role in the biotransformation of many drugs and toxicants. This usually results in the formation of metabolites that are less toxic than the parent compound; however, in some cases (e.g., the oxidation of ethylene glycol to glycolate and oxalate), the metabolites are more toxic than the parent compound.

Box 44-2 presents a partial list of potential nephrotoxicants. It should be noted that toxic insults to the kidney often can be caused by therapeutic agents, in addition to the better-known nephrotoxicants. Gentamicin and ethylene glycol are two of the most common causes of toxicantinduced ARF. Box 44-3 presents a partial list of ischemic causes of ARF. Leptospirosis is a common cause of ARF; the organisms colonize and proliferate within renal tubular epithelial cells and can lead to acute interstitial nephritis. Acute renal damage leading to failure can also occur in dogs with leptospirosis because of renal vasculitis and the development of swelling that further compromises renal blood flow. Acute renal failure has also recently been associated with ingestion of pet food containing contaminated wheat and corn gluten and rice protein concentrates. The investigation has focused on melamine and cyanuric acid as the major contaminants; however, melamine-related substances (e.g., ammelide and ammeline) may also be involved in the pathogenesis. It is thought that a chemical reaction between melamine and cyanuric acid produces insoluble crystals that form in the distal renal tubules of affected animals, compromising renal function. Clinical presentation is quite variable and ranges from severe ARF to mild azotemia associated with urineconcentrating deficits to no clinical signs. Crystalluria (round, yellow crystals with radiant striations that may resemble urate crystals) is observed in many cases. Identification of the crystals can be accomplished at veterinary diagnostic laboratories. Treatment of affected patients in largely symptomatic, long-term intravenous (IV) fluid therapy may be required for recovery in some cases.

In many cases, ARF inadvertently develops in the hospital setting in conjunction with the performance of diagnostic or therapeutic procedures. For example, ARF may be caused by hypotension and decreased renal perfusion associated with anesthesia and surgery or with the use of vasodilators or nonsteroidal antiinflammatory drugs (NSAIDs). Prolonged



BOX 44-2

## Partial List of Potential Nephrotoxicants in Dogs and Cats

# Therapeutic Agents Antimicrobials

Aminoglycosides

Cephalosporins

Nafcillin (especially in combination with anesthesia)

Polymyxins Sulfonamides Tetracyclines

#### Antifungals

Amphotericin B

#### **Anthelmintics**

Thiacetarsamide

#### Analgesics

Nonsteroidal antiinflammatory drugs

#### Heavy Metals

Lead Mercury Cadmium Chromium

#### **Organic Compounds**

Ethylene glycol Carbon tetrachloride Chloroform Pesticides Herbicides Solvents

#### **Pigments**

Hemoglobin Myoglobin

#### Intravenous Agents

Radiographic contrast agents

#### **Chemotherapeutic Agents**

Cisplatin Methotrexate Doxorubicin

#### **Anesthetics**

Methoxyflurane

#### Miscellaneous Agents

Hypercalcemia Snake venom Raisins/grapes



BOX 44-3

# Partial List of Potential Causes of Decreased Renal Perfusion/Ischemia in Dogs and Cats

Dehydration

Hemorrhage

Hypovolemia

Decreased oncotic pressure

Deep anesthesia

Increased blood viscosity

Sepsis

Shock/vasodilation

Administration of nonsteroidal antiinflammatory agents, decreased renal prostaglandin formation

Hyperthermia

Hypothermia

Burns

Trauma

Renal vessel thrombosis or microthrombus formation Transfusion reactions anesthesia with inadequate fluid therapy in older dogs and cats with preexisting, subclinical renal insufficiency is a frequent cause of renal ischemia and ARF in the hospital setting. Similarly, ARF frequently occurs in animals treated with potential nephrotoxicants such as gentamicin or amphotericin. The kidneys can maintain adequate renal perfusion pressure by autoregulation as long as the mean arterial blood pressure exceeds approximately 60 to 70 mm Hg. Renal blood flow and perfusion pressure must be maintained for glomerular filtration and cellular delivery of oxygen and nutrients to occur. Cellular swelling secondary to decreased Na/K pump activity results from the osmotic extraction of water from the extracellular space, causing the amount of water in the plasma to decrease. The consequences of a decreased amount of plasma water in the renal vasculature are red blood cell aggregation and vascular congestion and stasis, which tend to potentiate and perpetuate decreased glomerular blood flow and decreased oxygen and nutrient delivery. The common result of ischemic or toxicant-induced tubular cell swelling, injury, and death is nephron dysfunction leading to a decreased glomerular filtration rate

In ARF dysfunction and reduced glomerular filtration occur at the individual nephron level as a result of a combination of tubular obstruction, tubular backleak, renal arte-

riolar vasoconstriction, and decreased glomerular capillary permeability. Specifically, cellular debris within the tubule may inspissate and obstruct the flow of filtrate through the nephron. Alternatively, interstitial edema may compress and obstruct renal tubules. A backleak, or abnormal reabsorption of filtrate, occurs because of a loss of tubular cell integrity, allowing the filtrate to cross from the tubular lumen into the renal interstitium and subsequently the renal vasculature. Tubular backleak is facilitated by tubular obstruction because of the increased intratubular pressures proximal to the obstruction. The decreased resorption of solute and water by damaged proximal tubule segments results in the increased delivery of solutes and fluid to the distal nephron and macula densa in many nephrons, which causes afferent glomerular arteriole constriction. The exact mediators of this vasoconstriction are not known, but natriuretic factor, the reninangiotensin system, and thromboxane may be involved. A decrease in the permeability of the glomerular capillary wall also leads to a reduction in glomerular filtration. For example, aminoglycosides have been shown to decrease both the number and size of fenestrae in glomerular capillary endothelial cells, thereby decreasing the surface area available for ultrafiltration. The impaired glomerular capillary permeability that occurs in ARF often persists after vasoconstriction and renal blood flow have been corrected.

Acute tubular damage leading to ARF has three distinct phases: (1) initiation, (2) maintenance, and (3) recovery. During the initiation phase, therapeutic measures that reduce the renal insult can prevent the development of established ARF. In the initiation phase, individual tubules are damaged but overall renal function remains adequate. Acute tubular damage, occurring before the development of ARF, is suggested by renal tubular epithelial cells and casts in the urine sediment (discussed in more detail later). The maintenance phase is characterized by the development of tubular lesions and nephron dysfunction (i.e., renal azotemia and urineconcentrating deficits). Although therapeutic interventions during the maintenance phase are often life saving, they usually do little to diminish the severity of existing renal lesions, improve function, or hasten recovery. In the recovery phase, renal lesions are repaired and function improves. Tubular damage may be reversible if the tubular basement membrane is intact and viable epithelial cells are present. Although new nephrons cannot be produced and irreversibly damaged nephrons cannot be repaired, the functional hypertrophy of surviving nephrons may adequately compensate for the decrease in nephron numbers. Even if renal functional recovery is incomplete, adequate function may be reestablished.

# **Clinical Features and Diagnosis**

Clinical signs of ARF are often nonspecific and include lethargy, depression, anorexia, vomiting, diarrhea, and dehydration; occasionally, uremic breath or oral ulcers may be present. A diagnosis of ARF is suspected if azotemia develops acutely and is associated with persistent isosthenuria or minimally concentrated urine. Prerenal dehydration and



FIG 44-2

Ultrasonographic appearance of a kidney from a dog that ingested ethylene glycol. Notice the markedly increased renal cortical echogenicity. (Courtesy Dr. Phillip Steyn, Colorado State University, Fort Collins, Colo.)

azotemia superimposed on an inability to concentrate urine (e.g., Addison's disease, hypercalcemia, overzealous use of furosemide) initially mimics renal failure; however, in these prerenal cases, volume replacement results in resolution of the azotemia.

ARF occurs within hours or days of exposure to the insult. Unique clinical signs and clinicopathologic findings associated with ARF include enlarged or swollen kidneys, hemoconcentration, good body condition, active urine sediment (e.g., granular casts, renal epithelial cells), and relatively severe hyperkalemia and metabolic acidosis (especially in the face of oliguria; see Box 41-7). Clinical signs in an animal with ARF tend to be severe compared with those seen in an animal with CKD and similar magnitude of azotemia. Renal ultrasonographic findings in dogs and cats with ARF are usually nonspecific, with diffusely normal to slightly hypoechoic renal cortices. In animals with calcium oxalate nephrosis associated with ethylene glycol ingestion, the renal cortices can be very hyperechoic (Fig. 44-2). Doppler estimation of the resistive index (RI) in renal arcuate arteries is increased in many dogs with ARF; however, this method of evaluation must be more extensively correlated with the renal histopathologic changes before firm conclusions regarding the merits of the RI can be drawn.

Renal biopsy specimens from dogs and cats with ARF show proximal tubular cell degeneration, ranging from cloudy swelling to necrosis, with edema and mononuclear and polymorphonuclear leukocyte infiltration in the interstitium. Ethylene glycol and melamine-associated nephrotoxicity is frequently associated with intratubular crystals. Although toxicant-induced ARF cannot be histopathologically differentiated from ARF caused by ischemia in all cases, renal histologic findings are often helpful in establishing a prognosis. Evidence of tubular regeneration (e.g., flattened, basophilic epithelial cells with irregular nuclear size; mitotic figures; high nuclear/cytoplasmic ratios) and the finding of generally intact tubular basement membranes are good

prognostic findings and may be observed as early as three days after the insult. Conversely, large numbers of granular casts, extensive tubular necrosis, and interstitial mineralization and fibrosis with disrupted tubular basement membranes are poor prognostic signs. In addition to the renal histopathologic changes, the degree of functional impairment and, even more important, the response to therapy should be considered when formulating a prognosis.

# RISK FACTORS FOR ACUTE RENAL DAMAGE/FAILURE

Although the prevention of trauma (e.g., being hit by car) that may lead to shock and the development of renal ischemia or exposure to nephrotoxicants outside the hospital relies on client education and environmental control, an important aspect of the prevention of hospital-acquired ARF is the identification of patients at increased risk. Several risk factors that predispose dogs to the development of gentamicin-induced ARF have been identified (Box 44-4); however, it is likely that many of these factors also predispose dogs and cats to the development of other types of toxicantinduced ARF as well as ARF induced by ischemia. In many cases a combination of decreased renal perfusion or treatment with nephrotoxic agents in the context of more chronic, preexisting risk factors is responsible for the development of ARF in the hospital setting. Once the clinician detects predisposing risk factors, he or she can assess the risk: benefit ratio in individual cases in which an elective anesthetic procedure is considered or treatment with potentially nephrotoxic drugs is indicated. In some situations, predisposing risk factors can be eliminated or corrected before any potential renal insults occur.

Major categories of risk factors include disorders affecting renal perfusion, preexisting renal disease, electrolyte disturbances, treatment with nephrotoxic drugs, and dietary influences. Poor renal perfusion increases the risk of neph-



BOX 44-4

#### Risk Factors for Acute Renal Failure

Preexisting renal disease or renal insufficiency

Dehydration

Decreased cardiac output

Sepsis, pyometra

Disseminated intravascular coagulation (DIC)

Fever

Liver disease

Electrolyte abnormalities such as hypokalemia and hypercalcemia

Concurrent use of diuretics with potentially nephrotoxic drugs such as aminoglycosides

Concurrent use of potentially nephrotoxic drugs such as aminoglycosides, nonsteroidal antiinflammatory drugs, and intravenous radiographic contrast agents

Decreased dietary protein

Diabetes mellitus

rotoxic and ischemic damage to the kidney. Dehydration and volume depletion are perhaps the most common causes of decreased renal perfusion. Renal hypoperfusion can also be caused by decreased cardiac output, decreased plasma oncotic pressure, increased blood viscosity, or systemic vasodilation. In addition to decreased renal perfusion, volume depletion also leads to a decreased volume of distribution of nephrotoxic drugs and a decreased flow of tubular fluid. Decreased tubular flow, in turn, potentiates tubular resorption, which can increase the intratubular concentration of nephrotoxicants. Preexisting renal disease and advanced age, which is often associated with some degree of decreased renal function, may increase the potential for nephrotoxicity produced by several mechanisms. For example, the pharmacokinetics of potentially nephrotoxic drugs may be altered in the face of decreased renal function. Specifically, the excretion of gentamicin has been shown to be decreased in partially nephrectomized dogs with subclinical renal dysfunction. Animals with renal insufficiency or advanced age may also have reduced urine-concentrating ability and thus a decreased ability to compensate for dehydration. Preexisting renal disease may also compromise the production of vasodilatory prostaglandins. The resulting unbalanced vasoconstriction could result in decreased renal perfusion.

Studies in dogs have shown that reduced dietary potassium intake exacerbates gentamicin-induced nephrotoxicity, possibly because potassium-depleted cells are more susceptible to necrosis. It is important to note that an adverse effect of high-dose gentamicin treatment in dogs is an increase in the urinary excretion of potassium. It is possible that this could result in potassium depletion (especially if it occurs in combination with anorexia or vomiting) and thus increase the risk of gentamicin-induced nephrotoxicity. Because potassium is primarily an intracellular cation, any patient with prolonged anorexia, vomiting, or diarrhea may have whole-body potassium depletion even if serum potassium concentrations are within the normal range.

The administration of potentially nephrotoxic drugs or drugs that may enhance nephrotoxicity obviously increases the risk of ARF. For example, the concurrent use of furosemide and gentamicin in dogs is associated with an increased risk of ARF and an increased severity of ARF, should it occur. Furosemide probably potentiates gentamicin-induced nephrotoxicity by causing dehydration, reducing the volume of distribution of gentamicin, and increasing its renal cortical uptake. Fluid repletion minimizes but does not negate the additive effect of furosemide on gentamicin-induced nephrotoxicity in the dog because furosemide facilitates the tubular uptake of gentamicin independent of hemodynamic changes. By means of similar mechanisms, furosemide has been shown to enhance radiocontrast agent and cisplatin-induced nephrotoxicity in human beings.

The use of NSAIDs can also increase the risk of acute renal damage and ARF. In well-hydrated, healthy patients, NSAIDs are usually well tolerated. However, in situations associated with high renin concentration (e.g., sodium or volume depletion, hypotension, congestive heart failure, CKD) the potential for adverse effects on renal function increases. High renin states stimulate the production of angiotensin and aldosterone, which can, in turn, decrease renal blood flow and GFR. Normally, renal prostaglandins counteract this decrease in renal blood flow and GFR. However, in patients with CKD and those undergoing treatment with NSAIDs, the protective effects that prostaglandin has on renal blood flow and GFR may be compromised. Dogs appear to be particularly sensitive to NSAIDs such as ibuprofen and naproxen, which, in addition to ARF, may cause gastrointestinal tract ulceration. At one time, COX 2-specific inhibitors were thought to have less effect on renal blood flow; however, research shows that COX 2 enzymes are present or expressed in the canine kidney; therefore any NSAID, regardless of its COX specificity or sparing properties, has the potential to produce adverse renal effects. In particular, dogs express higher basal levels of COX 2 in the kidney than some other species and may be uniquely sensitive to the nephrotoxic effects of COX 2-selective drugs. There is also the concern that patients treated with angiotensin-converting enzyme inhibitors (ACEIs) may have increased risk of renal toxicity when treated with NSAIDs because some of the beneficial effects of ACEI are derived from kinin-stimulated production of prostaglandins. In one study of normal dogs treated with enalapril and tepoxalin, no alteration of GFR was noted.

Studies in healthy dogs have shown that the quantity of protein fed before a nephrotoxic insult can significantly affect the degree of renal damage and dysfunction. Highdietary-protein (27.3%) conditioning beginning 21 days before and continuing during gentamicin administration was found to reduce nephrotoxicity, enhance gentamicin clearance, and result in a larger volume of distribution compared with the findings in dogs fed medium (13.7%) or low levels of protein (9.4%). In addition, creatinine clearance and the renal elimination of gentamicin were preserved throughout 7 days of treatment in dogs fed a high-protein diet, whereas these parameters decreased during the treatment period in dogs fed a medium- or low-protein diet. Although dietary protein conditioning may not be practical in the clinical setting, it is important to realize that anorectic animals may be at increased risk for ARF as a result of decreased protein intake.

Risk factors are additive, and any complication occurring in high-risk animals increases the potential for ARF. By virtue of their diseases, animals in shock or with acidosis, sepsis, or major organ system failure are at increased risk for ARF, and these are also the animals that are likely to require anesthesia or chemotherapy, which is potentially damaging to the kidneys. For example, ARF is common in dogs with pyometra and *Escherichia coli* endotoxin-induced urine-concentrating defects. If fluid therapy is inadequate during anesthesia for ovariohysterectomy or during the recovery period, dehydration and decreased renal perfusion may result in ARF. Trauma, extensive burns, pancreatitis, diabetes mellitus, and multiple myeloma are examples of disorders associated with a high incidence of ARF in people. Addi-

tional clinical conditions that are thought to enhance the risk of ARF in dogs include vasculitis, fever, and prolonged anesthesia.

# MONITORING PATIENTS AT RISK FOR ACUTE RENAL DAMAGE/FAILURE

The recognition and appropriate management of renal injury in the initial phase of ARF are associated with improvement in prognosis; therefore animals receiving potentially nephrotoxic drugs and high-risk animals undergoing anesthesia should be monitored closely.

Along with blood pressure, urine production is an excellent parameter to monitor during anesthesia. Ideally, urine production should be greater than 2 ml/kg/h. Increased urinary excretion of protein, glucose (normoglycemic glucosuria), or casts and/or renal tubular epitheial cells may be an early indication of renal tubular damage in animals receiving potentially nephrotoxic drugs. As an alternative to standard clinicopathologic tests, the detection and quantification of urine enzymes (enzymuria) have been used to recognize early nephrotoxicity in the dog. Inasmuch as most serum enzymes are not filtered by the glomerulus because of their large molecular weight, enzymuria may be an indication of renal tubular leakage or necrosis. Several enzymes originate from specific cellular organelles and thus can serve as markers for damage to a specific site. For example, y-Glutamyl transpeptidase (GGT) originates from the proximal tubular brush border and N-acetyl glucosaminidase (NAG) is a lysosomal enzyme. Enzymuria usually precedes azotemia and decreased urine-concentrating ability associated with nephrotoxic proximal tubular injury by several days. The urine GGT: creatinine and NAG: creatinine ratios have been shown to accurately reflect 24-hour urine GGT and NAG excretion in dogs, if determined before the onset of azotemia. Baseline urine GGT:creatinine and NAG: creatinine ratios therefore should be determined in all dogs that are to receive potentially nephrotoxic drugs. Twofold to threefold increases in the GGT/creatinine or NAG/creatinine ratio over the baseline are suggestive of clinically relevant tubular damage. Drug therapy should be discontinued if this occurs.

#### **Treatment**

The goals of treatment of established ARF are to eliminate renal hemodynamic disorders and alleviate water and solute imbalances to give the nephrons additional time to repair and hypertrophy. A positive response to therapy is indicated by a decrease in the serum creatinine concentration and an increase in urine production. Induction of diuresis facilitates the management of ARF by decreasing serum urea nitrogen, phosphorus, and potassium concentrations and by lessening the likelihood of overhydration. Even though the GFR and renal blood flow may improve in response to diuresis, they are frequently unchanged, and the increased urine production is actually a result of decreased tubular resorption of filtrate (Table 44-1). Increased urine production alone does not indicate an improvement in GFR.



**TABLE 44-1** 

Hypothetical Comparison of the Glomerular Filtration Rate and Urine Production in Normal and Nonoliguric Acute Renal Failure States\*

NORMAL	ACUTE RENAL (L/DAY)	FAILURE (L/DAY)
Glomerular filtration rate	100	10
Tubular resorption	99	07
Urine production	1	03

<sup>\*</sup> These show the effect of tubular resorption on urine production in the face of decreased glomerular filtration.

Treatment guidelines for ARF are listed in Box 44-5. Most dogs and cats with ARF are dehydrated because of gastrointestinal fluid loss (e.g., vomiting) superimposed on their inability to concentrate urine. Replacement of these volume deficits will correct the prerenal component of the ARF and help protect against any additional ischemic renal tubular damage. Once the patient is rehydrated, establishing or augmenting diuresis can facilitate excretion of solutes that are reabsorbed and secreted by renal tubular cells (e.g., urca nitrogen and potassium). Increasing tubular flow rates and volumes will hinder reabsorption and favor secretion of solutes.

The large volume of fluid and rapid administration rate necessary in patients with ARF require that fluids be given intravenously. Jugular catheters or other central venous lines are ideal because they facilitate frequent blood sampling and infusion of hypertonic solutions (e.g., mannitol) and allow access for central venous pressure (CVP) measurement. Deficit fluid requirements should be replaced over the first 4 to 6 hours of treatment unless the patient has a cardiac disorder that requires a slower administration rate. A fluid bolus challenge of 20 ml/kg body weight given intravenously over 10 minutes can help assess the possibility of a subsequent volume overload. The CVP should not increase by more than 2 cm of water if the patient's cardiovascular function is normal. Because measurement of CVP is not always accurate or reproducible, results should always be interpreted in light of other parameters (e.g., patient's body weight, hematocrit, plasma total solids, and physical examination findings). The purpose of replacing volume deficits over the first 4 to 6 hours rather than over the normal 12 to 24 hours is to rapidly improve renal perfusion and decrease the likelihood of continued ischemic damage. Normal saline (0.9% solution) is the fluid of choice for rehydration unless the patient is hypernatremic, in which case a 0.45% saline with 2.5% dextrose solution should be used. The amount of fluid required to restore extracellular fluid deficits can be calculated by multiplying the estimated percentage of dehydration by the patient's body weight in kilograms.

During this rapid rehydration phase the patient should be closely observed for signs of overhydration. Frequent



BOX 44-5

#### Treatment Guidelines for Dogs and Cats with Acute Renal Failure

Discontinue all potentially nephrotoxic drugs; consider measures to decrease absorption (e.g., induction of emesis and administration of activated charcoal and sodium sulfate).

Start specific antidotal therapy if applicable (e.g., alcohol dehydrogenase inhibitors for ethylene glycol).

Identify and treat any prerenal or postrenal abnormalities. Start intravenous fluid therapy with normal saline solution

- or 0.45% saline solution in 2.5% dextrose:
- a. Rehydrate animal within 6 hours.
- Provide maintenance fluid and replace continuing fluid losses.

Assess volume of urine production.

Correct acid-base and electrolyte abnormalities; rule out hypercalcemic nephropathy.

If necessary, to increase urine production, provide mild volume expansion while monitoring urine volume, body weight, plasma total solids, hematocrit, and central venous pressure.

Administer diuretics, if necessary, to increase urine production:

- a. Mannitol or
- b. Furosemide

Base subsequent fluid volumes on urine production plus 20 ml/kg/24 h.

Consider peritoneal dialysis if there is no response to above treatment; biopsy kidney at time of dialysis catheter placement.

Control hyperphosphatemia:

- a. Phosphate-restricted diet and, if necessary,
- b. Enteric phosphate binders

Treat vomiting and gastroenteritis with:

- a. Metoclopramide,
- b. Trimethobenzamide, or
- c. Chlorpromazine

Treat gastric hyperacidity with H<sub>2</sub> blockers.

Provide caloric requirements (70 to 100 kcal/kg/day).

assessment of body weight, CVP, packed cell volume, and plasma total solids will help detect early overhydration. An increase in the CVP of  $\geq 5$  to 7 cm of water over baseline values suggests the likelihood of overhydration. Physical manifestations of overhydration include increased bronchovesicular sounds or overt crackles and wheezes, tachycardia, restlessness, chemosis, and scrous nasal discharge; however, these signs tend to be observed after the development of pulmonary edema. Overhydration in dogs and cats with oligoanuric ARF is a common complication that is extremely difficult to correct.

Urine production should be measured and electrolyte and acid-base status assessed during the period of rehydration. Urine production (ml/kg/hour) should be measured so that maintenance fluid needs can be accurately administered.



**TABLE 44-2** 

Hypothetical Examples of Daily Maintenance Fluid Requirements in Dogs and Cats

	NORMAL URINE PRODUCTION	OLIGURIC ARF	NONOLIGURIC ARF
Insensible	20	20	20
loss (ml/kg) Urine volume (ml/kg)	40	10	160
Total (ml/kg)	60	30	180

ARF, Acute renal failure.

Because approximately two thirds of normal maintenance fluid needs are due to fluid loss in urine, oliguric and nonoliguric patients can have large variations in their maintenance fluid needs (see Table 44-2). Metabolism cages, urinary catheters, and manual collection of voided urine are methods used to collect and measure urine volume. With regard to indwelling urinary catheters, strict aseptic technique and closed collection systems must be used. Because of the possibility of urinary tract infection, intermittent urinary bladder catheterization is usually recommended over indwelling catheterization for timed urine volume collections. In cats weighing the litter pan before and after voiding is a useful, although less accurate, method for assessing urine production. If an indwelling urinary catheter or a metabolism cage is not available, patients should be weighed in the same scale two or three times a day to assess fluid gain or

Initially, most patients with ARF have normal scrum sodium and chloride concentrations on account of isonatremic fluid loss. However, hypernatremia can develop after several days of therapy with fluids containing large amounts of sodium (0.9% NaCl, lactated Ringer's solution, and Normosol) and/or in association with sodium bicarbonate treatment of metabolic acidosis. If hypernatremia occurs, the use 0.45% NaCl with 2.5% dextrose fluids will usually correct the problem.

Disorders of calcium balance can also occasionally occur in patients with ARF. If moderate to severe hypercalcemia is observed, a primary hypercalcemic disorder (e.g., neoplasia or vitamin D<sub>3</sub> intoxication) should be considered as the cause of the renal failure. In most cases assessment of the ionized calcium concentration is preferable to measurement of the total calcium concentration. Immediate treatment for hypercalcemia includes rehydration with 0.9% NaCl followed by diuresis induced with furosemide. Glucocorticoids will also help lower calcium concentrations by decreasing intestinal absorption and facilitating excretion, but their use may interfere with the diagnosis of the underlying disorder (e.g., lymphoma). Intravenous bisphosphonates (pamidronate-Aredia, 1 mg/kg as a constant rate infusion (CRI) in

0.9% saline solution) are effective in lowering serum calcium concentration and do not affect the clinician's ability to diagnose the primary cause of hypercalcemia. Conversely, significant hypocalcemia can be observed in dogs and cats with ARF associated with ethylene glycol intoxication.

Oliguric ARF patients are at risk for hyperkalemia. Serum potassium concentrations greater than 6.5 to 7.0 mEq/L can cause cardiac conduction disturbances (bradycardia, atrial standstill, idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, asystole) and electrocardiographic changes (peaked T waves, prolonged PR intervals, widened QRS complexes, or the loss of P waves). Mild to moderate hyperkalemia typically resolves with administration of potassium-free fluids (dilution) and improved urine flow (increased excretion). More severe hyperkalemia (>7-8 mEq/ L) or hyperkalemia resulting in electrocardiographic (ECG) abnormalities should be treated with agents that rapidly decrease serum potassium concentrations or counteract the effects of hyperkalemia on cardiac conduction. Sodium bicarbonate (see discussion of dosage later in this chapter) helps correct metabolic acidosis and lower serum potassium concentration by exchanging intracellular hydrogen ions for potassium. Insulin can also be used to increase intracellular shifting of potassium. Regular insulin is administered intravenously at a dosage of 0.1 to 0.25 U/kg, followed by a glucose bolus of 1 to 2 g per unit of insulin given. Blood glucose monitoring should be maintained for several hours after administration of insulin because hypoglycemia may occur. Ten percent calcium gluconate (0.5-1.0 ml/kg administered intravenously over 10 to 15 minutes) will counteract the cardiotoxic effects of hyperkalemia without lowering the serum potassium and can be used in emergency situations. The effects of the aforementioned regimens are short-lived, and fluid and acid-base therapy to initiate and maintain a diuresis and maintain blood pH and bicarbonate within the normal range (discussed in more detail later in this chapter) are important to maintain potassium excretion and normokalemia.

Mild to moderate metabolic acidosis also generally resolves after fluid therapy, and specific treatment is usually not necessary unless the blood pH is less than 7.2 or the total  $CO_2/CO_3H$  is less than 12 mEq/L. Bicarbonate requirements can be calculated using the base deficit as determined from arterial blood gas, or an estimated base deficit [body weight (kg)  $\times$  0.3  $\times$  base deficit or  $(20-T\ CO_2)$  = mEq bicarbonate required]. Optimally, one half the calculated bicarbonate dosage should be administered intravenously over 15 to 30 minutes, and then acid-base parameters reassessed. Overzealous bicarbonate administration may result in ionized hypocalcemia, paradoxical cerebral spinal fluid (CSF) acidosis, and/or cerebral edema.

If signs of overhydration are not present and oliguria persists after apparent rehydration, mild volume expansion (3% to 5% of the patient's body weight in fluid) may be initiated inasmuch as dehydration of this magnitude is difficult to detect clinically. If volume expansion is attempted, the possibility of inducing overhydration increases and close

patient observation is necessary. Unfortunately, most patients that have oliguria will remain oliguric after rehydration and volume expansion.

In the past, diuretic therapy was frequently recommended in patients that were persistently oligoanuric despite appropriate fluid therapy. Compared with those patients with diminished urine production, polyuric ARF patients are thought to have less severe tubular injury, improved excretion of solutes that are reabsorbed or secreted (e.g., urea nitrogen and potassium), and less risk of developing overhydration and pulmonary edema. There is, however, no evidence that diuretic therapy will hasten the recovery from ARF or decrease mortality associated with ARF. In humans with established ARF, there is increasing evidence that diuretic therapy may actually be associated with increased risk of death and nonrecovery of renal function. If the choice is to use diuretics in dogs or cats with ARF, they should be used only after dehydration has been corrected and the patient has been volume expanded. Furosemide and mannitol are probably the diuretics of choice. Dopamine is not recommended because of its unpredictable effects on renal blood flow and GFR.

Furosemide blocks the reabsorption of chloride and sodium in the thick ascending limb of Henle, resulting in natriuresis and osmotic diuresis. The dose recommended for oligoanuric dogs and cats is 2 to 6 mg/kg IV q8h; however, in healthy dogs CRI of furosemide with a 0.66 mg/kg IV loading dose followed by 0.66 mg/kg/h resulted in more diuresis, natriuresis, and calciuresis and less kaliuresis than did intermittent bolus infusion.

Mannitol, in a 10% or 20% solution, has been recommended as an osmotic diuretic at a dose of 0.5 to 1.0 g/kg, given intravenously as a slow bolus over 15 to 20 minutes. Urine output should increase within 1 hour if the treatment is effective. A second bolus may be attempted, but the potential for volume overexpansion and complications such as pulmonary edema increases considerably if urine production does not increase. As an osmotic agent, mannitol may decrease tubular cell swelling, increase tubular flow, and help prevent tubular obstruction or collapse. In healthy cats the renal effects of mannitol, when used as an adjunct to fluid therapy, are superior to those of furosemide and dopamine combination. The use of mannitol is contraindicated in an overhydrated patient because the resultant increase in intravascular volume may precipitate pulmonary edema.

Whether or not diuresis can be established, fluid therapy should be tailored to match urine volume and other losses, including insensible losses (e.g., water loss caused by respiration) and continuing losses (e.g., fluid loss caused by vomiting or diarrhea). Insensible losses are estimated at 20 ml/kg/day. Urine output is quantitated for 6- to 8-hour intervals, and that amount is replaced over an equivalent subsequent time period. The volume of fluid loss resulting from vomiting and/or diarrhea is estimated, and that amount is added to the 24-hour fluid needs of the patient. Fluid losses or gains can also be indirectly estimated by weighing the patient 2 to

3 times a day on the same scale. If hypernatremia and hyperkalemia are not present and a diuresis has been established, polyionic maintenance fluids (e.g., lactated Ringer's solution, Normosol) should be used. In the recovery phase of ARF, urine volume and electrolyte losses can be great. Potassium supplementation may be necessary, especially if the patient is vomiting or anorectic.

Control of nausea and vomiting in dogs and cats with ARF is important to facilitate caloric intake. In addition, the inability to control vomiting is discouraging to owners and may result in a hastened decision for cuthanasia. (Please see the section on management of chronic kidney disease for specific recommendations for the treatment of nausea and vomiting.)

When fluid therapy is successful in inducing or maintaining diuresis, the daily volume of fluid administered to the patient will eventually need to be decreased. Indications for tapering IV fluid volume include the following: (1) significant decreases in BUN and phosphorus concentrations, (2) control of vomiting and diarrhea, and (3) improved mood and renewed interest in eating and drinking. These indications rarely occur before 5 or 6 days of intense fluid therapy/ diuresis and may require 10 or more days of treatment. Gradually reducing maintenance fluid requirements by 25% each day is usually recommended for fluid tapering. If the patient loses weight or increases in packed cell volume, total protein, and BUN and/or creatinine concentrations are observed, fluid therapy tapering should be discontinued and the previous maintenance volume reinstated for at least 48 hours.

Peritoneal or hemodialysis should be considered in patients with severe, persistent uremia, acidosis, or hyperkalemia. Dialysis may also be used to treat overhydration and hasten elimination of dialyzable toxicants. Renal biopsy should be performed if the diagnosis is in doubt, if the patient does not respond to therapy within 3 to 5 days, or if dialysis is considered. The long-term prognosis for dogs or cats with ARF is usually fair to good if the patient survives the period of renal tubular regeneration and compensation; however, several weeks may be required for renal function to improve. Animals with moderate to severe renal damage may require many weeks for renal repair, and the prolonged time required for recovery results in a poor prognosis. The severity of the initial azotemia/uremia, the response to fluid therapy, and assessment of renal histopathologic lesions are the most important prognostic indicators early in the course of ARF.

# CHRONIC KIDNEY DISEASE

## **Etiology and Pathogenesis**

Unlike ARF, the cause of CKD is usually difficult to determine. Because of the interdependence of the vascular and tubular components of the nephron, the end-point of irreversible glomerular or tubular damage is the same. A morphologic heterogeneity among nephrons exists in the



# Potential Causes of Chronic Kidney Disease in Dogs and Cats

#### Immunologic Disorders

Systemic lupus erythematosus

Glomerulonephritis

Vasculitis (e.g., feline infectious peritonitis)

# **Amyloidosis**

# Neoplasia

Primary

Secondary

**Nephrotoxicants** 

Renal Ischemia

Inflammatory or Infectious Causes

Pyelonephritis

Leptospirosis

Renal calculi

#### Hereditary and Congenital Disorders

Renal hypoplasia or dysplasia

Polycystic kidneys

Familial nephropathies (Lhasa Apsos, Shih Tzus, Norwegian Elkhounds, Rottweilers, Bernese Mountain Dogs, Chow Chows, Newfoundlands, Bull Terriers, Pembroke Welsh Corgis, Chinese Shar-Peis, Doberman Pinschers, Samoyeds, Golden Retrievers, Standard Poodles, Soft Coated Wheaten Terriers, Cocker Spaniels, Beagles, Keeshonds, Bedlington Terriers, Cairn Terriers, Basenjis, Abyssinian cats)

Urinary Outflow Obstruction Idiopathic

chronically diseased kidney, with the changes ranging from severe atrophy and fibrous connective tissue replacement to marked hypertrophy. The histopathologic changes are not process-specific, and therefore the cause is usually unknown. Nevertheless, recent studies have shown that primary glomerular disorders are a major cause of CKD in the dog. Because glomerular filtration *in toto* is uniformly reduced, CKD may be considered a single pathologic entity, although many diverse pathways can lead to this end-point. Potential causes of CKD are listed in Box 44-6.

The pathophysiology of CKD can be considered at both the organ and systemic level. At the level of the kidney, the fundamental pathologic change that occurs is a loss of nephrons and decreased GFR. Reduced GFR, in turn, results in increased plasma concentrations of substances that are normally eliminated from the body by renal excretion. Many substances have been shown to accumulate in the plasma of patients with CKD (Box 44-7). The constellation of clinical signs known as the *uremic syndrome* is thought to occur, at least in part, as a result of increasing plasma concentrations



BOX 44-7

Substances that Can Increase in Concentration in the Plasma of Dogs and Cats with Renal Failure

Amino acids

Ammonia

Aromatic and aliphatic amines

Creatinine

Cyclic adenosine monophosphate

Gastrin

Glucagon

Growth hormone

Guanidinium compounds

Indoles

Parathyroid hormone

**Peptides** 

**Phenols** 

**Phosphate** 

**Polyols** 

Purine and pyrimidine derivatives

Renin

Ribonuclease

Urea

Uric acid

of these substances. Components of the uremic syndrome include sodium and water imbalance, anemia, carbohydrate intolerance, neurologic disturbances, gastrointestinal tract disturbances, osteodystrophy, immunologic incompetence, and metabolic acidosis.

In addition to excreting metabolic wastes and maintaining fluid and electrolyte balance, the kidneys also function as endocrine organs and catabolize several peptide hormones. Therefore hormonal disturbances also play a role in the pathogenesis of CKD. For example, the decreased production of erythropoietin (EPO) and calcitriol in animals with CKD contributes to the development of nonregenerative anemia and hyperparathyroidism. Conversely, decreased metabolism and increased concentrations of parathyroid hormone (PTH) and gastrin contribute to the development of hyperparathyroidism and gastritis, respectively.

Some of the pathophysiologic changes that occur in CKD are brought about by compensatory mechanisms. The osteodystrophy of CKD occurs secondary to hyperparathyroidism, which develops in an attempt to maintain normal plasma calcium and phosphorus concentrations. Similarly, the GFR of intact hypertrophied nephrons increases in animals with CKD in an attempt to maintain adequate renal function; however, proteinuria and glomerulosclerosis in these individual nephrons, leading to additional nephron damage and loss, may be consequences of this hyperfiltration (Fig. 44-3).

#### **Clinical Features and Diagnosis**

Unlike ARF, CKD develops over a period of months or years, and its clinical signs are often relatively mild for the magni-

tude of the azotemia. Unique signs of CKD include a history of weight loss, polydipsia-polyuria, poor body condition, nonregenerative anemia, and small and irregularly shaped kidneys. A diagnosis of CKD is usually based on a combination of compatible historical, physical examination, and clinicopathologic findings. Plain radiographs can confirm the presence of small kidneys. Renal ultrasonography will usually show diffusely hyperechoic renal cortices with loss of the normal corticomedullary boundary. The increased cortical echogenicity results from replacement of the irreversibly damaged nephrons with fibrous connective tissue. Radiographic studies and ultrasonography can also help identify or rule out potentially treatable causes of CKD, such as pyelonephritis and renal urolithiasis. Renal biopsy is not routinely performed in animals with CKD unless the diagnosis is in question. Renal histopathologic preparations will show some combination of a loss of tubules with replacement fibrosis and mineralization, glomerulosclerosis and glomerular atrophy, and foci of mononuclear cells (small lymphocytes, plasma cells, and macrophages) within the interstitium in association with fibrous connective tissue replacement.

# Primary renal insult (glomerular, tubular, vascular, or interstitial) Decreased number of nephrons High dietary protein Increased tubular ammoniagenesis Hypertension Soft tissue mineralization Increased single nephron glomerular filtration rate (hyperfiltration) Increased protein loss per Mesangial cell injury intact nephron Glomerular hyalinization and sclerosis

**FIG 44-3**Proposed pathogenesis of progressive loss of nephrons in chronic kidney disease.

# STAGING CHRONIC KIDNEY DISEASE

Once a diagnosis of CKD has been established and fluid therapy has resolved any prerenal azotemia, staging the disease process can help clinicians focus their diagnostic and therapeutic efforts. The International Renal Interest Society (IRIS) was created to advance the scientific understanding of kidney diseases in small animals at the Eighth Annual Congress of the European Society of Veterinary Internal Medicine in Vienna, Austria in 1998. Seventeen independent veterinary nephrologists from eight countries serve on the IRIS Board, with the mission of helping practitioners better diagnose, understand, and treat canine and feline renal disease. Table 44-3 was developed by the IRIS Board as guide to staging canine and feline CKD.

Scrum creatinine concentrations must always be interpreted in light of the patient's urine specific gravity and physical examination findings to rule out prerenal and postrenal causes of azotemia. The CKD stages are further classified by the presence or absence of proteinuria and systemic hypertension (Table 44-4).

The classic diagnosis of renal failure based on renal azotemia (persistent azotemia superimposed on the inability to



TABLE 44-4

IRIS CKD Substaging System for Proteinuria and Hypertension

C. A CCIPICATION
CLASSIFICATION
Nonproteinuric
Borderline proteinuric
Proteinuric
CLASSIFICATION
Normotensive
Borderline hypertensive
Hypertensive

IRIS, International Renal Interest Society; CKD, chronic kidney disease.



TABLE 44-3

IRIS CKD Staging System for Dogs and Cats

SERUM CREATININE CONCENTRATION	STAGE I NONAZOTEMIC CKD	STAGE II MILD RENAL AZOTEMIA	STAGE III MODERATE RENAL AZOTEMIA	STAGE IV SEVERE RENAL AZOTEMIA
mg/dl (cats)	<1.6	1.6-2.8	2.9-5.0	>5.0
mg/dl (dogs)	<1.4	1.4-2.0	2.1-5.0	>5.0

concentrate urine) pertains to CKD stages II through IV. Stage I CKD (nonazotemic CKD) could be diagnosed in cats and dogs with persistent proteinuria, urine-concentrating deficits, increases in serum creatinine concentration over time even if the values remain in the normal range (e.g., serum creatinine concentration that increases form 0.6 to 1.2 mg/dl could indicate a 50% reduction in GFR), or abnormal renal palpation or renal ultrasonographic findings.

# **Further Diagnostics and Treatment**

In general, the diagnostic approach to a patient in which CKD has been identified and staged is focused on three areas: (1) characterization of the renal disease, (2) characterization of the stability of the renal disease and renal function, and (3) characterization of the patient's problems associated with the decreased renal function (Fig. 44-4). Further definition of the renal disease (beyond a standard minimum database) could include, for example, quantification of proteinuria, measurement of blood pressure, urine culture, kidney imaging, and possibly kidney biopsy. The stability of the renal function may be assessed by serial monitoring of abnormalities identified during the initial evaluation of the renal disease. This monitoring should always include serial serum biochemistry profiles, urinalyses, quantification of proteinuria, and measurement of blood pressure, but it may also include follow-up urine cultures and ultrasonographic examinations. Characterization of the renal disease and its stability is most important in the earlier stages of CKD, when appropriate treatment has the greatest potential to improve or stabilize renal function. Characterization of the patient's problems becomes more important in the later stages of CKD, when clinical signs tend to be more severe. In the later stages of CKD, diagnostic (and subsequent therapeutic) efforts should be directed at the anorexia, vomiting, acidosis, potassium depletion, hypertension, anemia, and related signs.

Similar to the diagnostic approach to CKD, the therapeutic approach should also be tailored to fit the patient's stage of disease. For example, disease-specific treatments for neph-

roliths or bacterial pyelonephritis as well as treatments designed to slow the progression of renal disease (so-called renoprotective treatments) will be of most value in the earlier stages of CKD. Examples of renoprotective treatments include dietary change designed to reduce serum phosphorus concentrations and ACEIs designed to normalize systemic and intraglomerular blood pressures and reduce proteinuria. In the later stages of CKD, treatment tends to be focused on ameliorating the patient's clinical signs associated with the decreased renal function.

Specific treatment in patients with CKD is directed at the primary cause of the kidney disease. Although it may not be possible to identify the primary cause of the CKD, specific treatment have the potential to reduce the magnitude of subsequent renal damage. As an example, bacterial pyelonephritis can cause or complicate CKD, and the condition can be specifically treated with appropriate antibiotic therapy. The prevalence of urinary tract infection (UTI) increases in older dogs and cats, and especially dogs and cats with CKD, because the antibacterial properties of the urine decline as its concentration decreases. In a study of cats with naturally occurring CKD, 29% had occult UTI. Bacterial infection of the renal pelvis and parenchyma (i.e., pyelonephritis) can then result from an ascending lower UTI. Initially with ascending UTI, the renal cortex is not affected; however, as chronic pyelonephritis develops, the entire kidney may become involved. Pyclonephritis also can precipitate the development of renal calculi, and, conversely, renal calculi can increase the risk of pyelonephritis. Long-term antibiotic therapy based on culture and sensitivity may halt the renal damage associated with pyelonephritis; however, if renoliths are present, antibiotic therapy alone is usually ineffective. Calcium oxalate uroliths are the most common type of renoliths in older cats, and because they cannot be dissolved, surgery is necessary for stone removal. Anesthesia and surgery, however, have the potential to further compromise renal function in the cat with CKD. In most cases, the patient is closely monitored for obstructive uropathy and surgery

	Stage I	Stage II	Stage III	Stage IV
Specific Renal Disease Investigation and Treatment	<b>A</b>	<b>A</b>	<b>A</b>	<b>A</b>
Assessment of Renal Disease Progression and Initiation of Renoprotective Treatment	<b>A</b>	<b>A</b>	<b>A</b>	<b>A</b>
Assessment and Treatment of Patient Problems	<b>A</b>	<b>A</b>	<b>A</b>	<b>A</b>

FIG 44-4

Prioritization of diagnostic and treatment efforts based on the stage of chronic kidney disease. The larger the arrowhead, the higher the priority.

is not performed unless an obstruction develops. Concurrent pyelonephritis that cannot be resolved with antibiotic treatment is another potential indication for surgical intervention.

Similar to bacterial pyelonephritis, hypertension (HT) can cause or complicate CKD. Gradual reduction of dietary salt intake is often recommended as the first line of treatment for HT; however, no studies document the efficacy of dietary salt reduction in lowering blood pressure in dogs or cats. In many cases vasodilators (ACEI and calcium channel blockers [CCBs]) may be necessary to control hypertension. Although ACEIs are usually recommended for HT associated with CKD in dogs, amlodipine is often recommended as the first-choice antihypertensive medication for cats. Recent studies, however, have raised the concern that amlodipine as a monotherapy in animals with renal disease may expose the glomeruli to higher pressures because of efferent arteriolar constriction caused by local increases in renin-angiotensinaldosterone system activity. If so, cats with renal disease should benefit from therapy with both ACEIs and CCBs. Cats with CKD are mild to moderate HT should be treated with an ACEI (e.g., benazepril: 0.5 to 1.0 mg/kg q24h) because of the positive effects on intraglomerular hypertension and proteinuria. In cats with severe HT (systolic blood pressure >180 mm Hg) or cats in which HT persists despite ACEI treatment, amlodipine (0.625 to 1.25 mg/cat q24h) treatment should be initiated. Several studies have documented renoprotective effects of ACEIs in dogs and cats with naturally occurring CKD.

Direct-acting vasodilator drugs such as ACEIs and CCBs are the most successful in achieving acute reduction of blood pressure, but sympathetic nervous system—mediated increases in heart rate and aldosterone-mediated sodium and water retention may modulate the effects of the vasodilation over time. Combining antihypertensive treatments with different modes of action may block the compensatory effects caused by one medication when used alone. For example, diuretics, aldosterone antagonists, and  $\beta$ -blockers, which may have minimal antihypertensive effect alone, may produce additive effects when given in combination with ACEIs or CCBs. Overall, the risk of target organ damage in the eyes, brain, kidneys, and heart is thought to be minimal if systolic blood pressure is <150 mm Hg (Table 44-5).

In many dogs and cats with stage II to IV CKD, renal lesions progress and renal function deteriorates (see Figure 44-1). Progressive loss of function as well as the rate of decline are monitored by longitudinal measurement of serum creatinine concentrations. In addition to the antihypertensive treatment discussed previously, ACEIs (to control intraglomerular hypertension and proteinuria) and dietary phosphorus restriction are examples of so-called renoprotective treatments. Reduction of dietary phosphorus is one of the cornerstones of management of CKD and can be accomplished by feeding specifically formulated diets for CKD. From a practical standpoint, dietary phosphorus reduction is combined with dietary protein reduction (discussed in more detail later). If, after 3to 4 weeks of dietary



**TABLE 44-5** 

Risk of Target Organ Damage Associated with Hypertension in Dogs and Cats

SYSTOLIC BLOOD PRESSURE (MM HG)	DIASTOLIC BLOOD PRESSURE (MM HG)	RISK LEVEL	
<150	<95	Minimal	
150-159	95-99	Low	
160-1 <i>7</i> 9	100-119	Moderate	
≥180	≥120	High	

phosphorus reduction, serum phosphorus concentrations remain high, enteric phosphate-binding gels containing calcium acetate, calcium carbonate, or aluminum hydroxide should be administered with meals (initial dosage of 30 mg/kg body weight with the dosage increased as needed to achieve normophosphatemia).

Hyperphosphatemia in patients with CKD occurs as a result of decreased renal excretion of phosphates. Concurrently, decreased renal production of the active form of vitamin D, decreases intestinal absorption of calcium, which, in conjunction with impaired renal reabsorption of calcium, decreases plasma ionized calcium concentrations. Decreased vitamin D<sub>3</sub> and serum calcium concentrations stimulate PTH secretion, which facilitates renal excretion of phosphorus and increases serum calcium concentrations by increasing renal calcium reabsorption and calcium absorption from bones and the gastrointestinal tract. The disadvantages of this hyperparathyroidism, however, can be severe and include osteodystrophy, bone marrow suppression, and soft tissue mineralization. Soft tissue mineralization occurs predominantly in damaged tissue, and if mineralization occurs in renal tissue, the result may be a progressive decline in renal function. If the product of the serum calcium and phosphorus concentrations is greater than 50 to 70 mg/dl, the patient is at risk for soft tissue mineralization. Studies in dogs and cats with remnant kidney CKD have shown that normal dietary phosphorus intake is associated with microscopic renal mineralization and fibrosis, and these changes were prevented by reducing dietary phosphorus. Similarly, in dogs and cats with naturally occurring CKD, feeding a diet specifically formulated to meet their needs, together with phosphate-binding drugs, if required, controls hyperphosphatemia and secondary renal hyperparathyroidism and is associated with a prolonged survival time. Physiologic doses of calcitriol may also be beneficial in dogs and cats with hyperparathyroidism and hyperphosphatemia associated with CKD. In a prospective, randomized, controlled clinical trial in dogs with spontaneous CKD (stages III and IV), calcitriol treatment (initial dose of 2.5 ng/kg/day that was adjusted within the range of 0.75 to 5.0 ng/kg/day according to serial determination of ionized calcium and PTH concentrations) resulted in decreased all-cause mortality and prolonged survival compared with placebo treatment. Calcitriol should not be administered until hyperphosphatemia has been controlled with diet and enteric binders. In addition, if the Ca X Phos product exceeds 60 to 70 mg/dl, calcitriol should not be used because of the risk of soft tissue mineralization. Serial serum calcium determinations are recommended in dogs and cats receiving calcitriol to help prevent hypercalcemia, especially if the patient is also receiving a calcium-containing enteric phosphorus binder.

Diagnosis and management of proteinuria in dogs and cats with CKD should be accomplished in a step-wise fashion. Because the specificity of the dipstick screening test for proteinuria in both dogs and cats is poor, confirmation of proteinuria should be accomplished with a more specific follow-up test, such as the sulfosalicylic acid (SSA) turbidimetric test, urine protein: creatinine ratio, or canine or feline specific albuminuria assay (see Chapter 42). The second step in assessment of proteinuria is to determine its origin. Proteinuria of renal origin can adversely affect the prognosis of dogs and cats with CKD, and therefore physiologic or benign proteinuria and prerenal and postrenal proteinuria should be ruled out. Subsequently, via serial monitoring, the clinician should determine whether the proteinuria is persistent or transient. Persistent proteinuria is defined as at least two positive tests at 2-week intervals. Relatively mild proteinuria in dogs and cats with spontaneous chronic renal failure appears to be a negative predictor of survival. In azotemic patients persistent proteinuria of renal origin with a urine protein: creatinine ratio > 0.4 (cats) or > 0.5 (dogs) should be treated with an ACEI and/or dietary protein reduction (discussed in more detail later).

Symptomatic treatment becomes a higher priority in the later stages of CKD, when the renal failure and uremia have a more pronounced effect on the patient's quality of life. In addition to phosphorus restriction, dietary management includes protein reduction (dietary protein is reduced not restricted in these diets; restriction of any dietary component generally means feeding less than the daily requirements), salt reduction, n-3 fatty acid supplementation, and alkalinization. Feeding specifically formulated renal failure diets not only may allow the animal to live more comfortably with decreased renal function but also may significantly prolong survival. Ideally, dietary protein reduction allows all essential amino acid requirements to be met without excesses. This is accomplished by feeding smaller quantities of high biological value protein and results in a decreased need for renal clearance of urea and other nitrogenous metabolites. When feeding reduced protein diets, the clinician must remember that the energy requirements of the body have a higher priority than does protein anabolism; therefore, if the available carbohydrates and fats are insufficient to meet caloric requirements, endogenous proteins will often be used as a source of energy. Catabolism of endogenous proteins for energy increases the nitrogenous waste that the kidney must excrete and exacerbates the clinical signs of renal failure.

A good recommendation for dietary protein reduction for both dogs and cats is to feed the maximum amount of high biological value, highly digestible protein that the animal can tolerate at his/her level of renal function. A favorable response to therapy consists of stable body weight and serum creatinine and albumin concentrations and decreasing serum urea nitrogen and phosphorus concentrations. Moderate dietary protein reduction should be employed early in the course of renal failure, and use of markedly reduced protein diets should be reserved for patients that are refractory to moderate dietary protein reduction.

Most diets for CKD are alkalinizing diets; however, potassium citrate or sodium bicarbonate, given orally to effect, may be indicated if the patient remains acidemic (total CO<sub>2</sub> < 12 mEq/L) 2 to 3 weeks after diet change. Oral potassium citrate supplementation may also prevent hypokalemia and potassium depletion in cats with CKD. Anorexia; highprotein, acidifying diets; polyuria-polydipsia; and vomiting can all contribute to potassium depletion; however, only 20% to 30% of cats with CKD have hypokalemia as an initial clinicopathologic finding. Potassium is predominantly an intracellular cation, and approximately 95% of total body potassium is present in skeletal muscle; therefore serum potassium concentrations may not accurately reflect total body potassium stores, especially in the early stages of potassium depletion. It has been documented that cats with CKD have lower muscle potassium concentrations and higher serum potassium concentrations than do normal cats. This data may suggest the need for oral potassium supplementation early in the course of CKD in cats. Generalized muscle weakness is the primary clinical sign associated with hypokalemia/potassium depletion. Muscle weakness usually resolves within 1 to 5 days after initiation of oral potassium supplementation.

Vomiting and anorexia are common in dogs and cats with CKD and can often result in decreased caloric intake. Causes of vomiting and anorexia include (1) stimulation of chemoreceptor trigger zone by uremic toxins, (2) decreased excretion of gastrin and increased gastric acid secretion (plasma gastrin concentrations in cats with chronic renal failure may be as high as 20 times the normal concentrations), and (3) gastrointestinal irritation secondary to uremia. Vomiting may be treated with metoclopramide, which blocks the chemoreceptor trigger zone. Metoclopramide also increases gastric motility and emptying without causing gastric acid secretion and is the drug of choice for vomiting associated with renal failure. H2 receptor blockers (famotidine or ranitidine) have been shown to effectively decrease gastric acid secretion, which may attenuate vomiting in CKD. Oral ulcers, stomatitis, and glossitis may occur as a result of gastritis and vomiting or the effect of uremic toxins on mucosal membranes and will often also result in anorexia. If vomiting has been controlled but anorexia persists, placement of a gastrostomy or esophagostomy tube will often facilitate the maintenance of caloric intake and hydration status. In many cases without feeding tubes, fluid therapy with polyionic solutions, given intravenously or subcutaneously in the hospital or subcutaneously by owners at home (10 to 50 ml/kg subcutaneously every 1 to 3 days), will help improve the patient's quality of life.

The nonregenerative anemia observed in dogs and cats with CKD occurs as a result of a combination of decreased EPO production, shortened red blood cell survival, gastrointestinal tract blood loss, and the effects of uremic toxins such as PTH on erythropoiesis. In addition, nutritional deficiencies (e.g., vitamins B<sub>6</sub> and B<sub>12</sub>, niacin, and folic acid) and iron depletion can contribute to the anemia associated with CKD. Anabolic steroids are usually of little benefit; however, treatment with recombinant human EPO in dogs and cats with CKD and anemia has generally been successful. Although not approved for use in veterinary medicine, the dosage that has been recommended is 100 U/kg of recombinant EPO given subcutaneously three times weekly. The dose interval is lengthened once a target packed cell volume is achieved (approximately 40% in dogs and 35% in cats). Usually, a dosage of 75 to 100 U/kg once or twice weekly is sufficient for maintenance. This treatment, in addition to increasing the packed cell volume, often results in increased appetite, weight gain, increased strength, and an improved sense of well-being. It should be noted, however, that antibodies may form in dogs and cats treated with human recombinant products. Studies show that antirecombinant EPO-binding antibodies will develop in approximately 25% to 30% of dogs and cats and that these antibodies may also react with endogenous EPO, making the animal transfusion dependent. Development of anti-r-HuEPO antibodies should be suspected in patients with a sudden decrease in packed cell volume. Iron deficiency; external blood loss; hemolytic disorders; and concurrent infectious, inflammatory, or neoplastic diseases should be ruled out in such patients. The absence of peripheral reticulocytes and severe erythroid hypoplasia (M:E ratio >10) on bone marrow cytology is compatible with the presence of anti-r-HuEPO antibodies. Iron supplementation (iron dextran: 10 mg/kg administered intramuscularly every 3 to 4 weeks) should be employed during recombinant EPO treatment because of the rapid initiation of erythropoiesis and marginal depletion of iron stores that occur in animals with CKD. Until canine and feline recombinant EPO become commercially available, treatment with human recombinant products should be reserved for those animals with weakness and lethargy attributable to their anemia.

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# CHAPTER A Urinary Tract Infections

### CHAPTER OUTLINE

### URINARY TRACT INFECTIONS

Etiology and Pathogenesis
Host Defense Mechanisms
Complicated Versus Uncomplicated Urinary Tract
Infections
Relapses Versus Reinfections
Clinical Features
Treatment

### URINARY TRACT INFECTIONS

Bacterial infections of the urinary tract occur more frequently in dogs than in cats. Although inflammatory disease of the lower urinary tract is common in cats, bacterial infections are rare. Fewer than 2% of the cases of lower urinary tract disease (LUTD) in cats are caused by a primary urinary tract infection (UTI). Most of the UTIs in dogs involve bacterial inflammation of the lower urinary tract (bladder, urethra); however, the ascension of bacteria into the ureters and kidneys is a potential sequela of lower UTIs. Compared with the prevalence of bacterial UTIs, mycoplasmal, chlamydial, viral, and fungal UTIs are rare in dogs. Most bacterial infections of the lower urinary tract respond quickly to appropriate antibiotic treatment; however, UTIs associated with defects in the host immune system (complicated UTIs) often fail to respond to antibiotic therapy, or the infection relapses shortly after antibiotic withdrawal.

### **Etiology and Pathogenesis**

The most common bacterial pathogens associated with UTIs in the dog include Escherichia coli, Staphylococcus, Streptococcus, Enterococcus, Enterobacter, Proteus, Klebsiella, and Pseudomonas organisms. E. coli is the most common isolate from canine and feline urine (Table 45-1). Although UTIs usually involve a single organism, as many as 20% to 30% may be mixed bacterial infections (i.e., two or more species). Most bacterial UTIs are thought to be caused by intestinal or cuta-

neous flora that ascend through the urethra to the bladder. Although many enteric organisms are anaerobes, the oxygen tension in urine probably inhibits the growth of strict anaerobic bacteria; therefore anaerobes rarely cause UTIs.

Bacterial virulence of invading organisms is a major factor that determines whether a UTI becomes established (Box 45-1). The ability of bacteria to adhere to the epithelial surface of the urinary tract prevents bacterial washout during voiding and allows bacteria to proliferate between urine voidings. Infection of the urinary tract usually involves bacterial colonization of the genitalia, migration of the bacteria along the urethra, and adherence of the organisms to the uroepithelium. Uroepithelial adherence is facilitated by fimbriae, which are rigid, filamentous, proteinaceous appendages found on many gram-negative bacteria. Other factors that increase bacterial virulence include capsular K antigens, which interfere with opsonization and phagocytosis, and O antigens in endotoxin, which decrease smooth muscle contractility. The latter may stop ureteral peristalsis and facilitate the ascension of bacteria from the bladder to the kidney. E. coli isolates from dogs have a greater ability to produce colicins (resulting in increased vascular permeability), hemolysins (increasing their invasiveness through tissue damage), and [-lactamase (causing resistance to ]-lactam antibiotics) and to ferment dulcitol (which is associated with resistance to phagocytosis), but they have a decreased ability to agglutinate red blood cells (RBCs; associated with uroepithelial adherence) compared with human E. coli isolates. Finally, cell wall-deficient bacterial variants may thrive in hypertonic environments such as the renal medulla and urine, where white blood cell (WBC) migration and phagocytosis may be compromised.

Bacterial resistance to antimicrobial drugs may result from inherent resistance, from mutation and selection, or from the transfer of resistance factors (R factors) between organisms through DNA transfer. An entire bacterial population can acquire resistance by genetic transfer after only one dose of an antibiotic. The R factor phenomenon has been identified in gram-negative bacteria, including *E. coli, Enterobacter, Klebsiella*, and *Proteus*. R factor resistance to multiple drugs is common, and R factors are known to



**TABLE 45-1** 

Approximate Percentages of Bacterial Isolates in Dogs with Urinary Tract Infections

ISOLATES	PERCENTAGE OF TOTAL		
E. coli	45		
Staphylococcus spp.	13		
Proteus spp.	10		
Enterococcus	8		
Klebsiella spp.	7		
Streptococcus spp.	6		
Enterobacter spp.	3		
Pseudomonas spp.	3		
Other organisms	5		



BOX 45-1

### Factors Affecting Bacterial Virulence

Fimbriae—facilitate attachment to uroepithelium Capsular K antigens—increase invasiveness and interfere with opsonization and phagocytosis

O antigens in endotoxin—decrease smooth muscle contractility

Cell wall-deficient bacterial variants—can exist in hypertonic environments (urine, renal medulla) where host defense mechanisms may be compromised

Colicins-increase vascular permeability

Hemolysins—increase invasiveness through tissue damage β-Lactamase—causes resistance to β-lactam antibiotics Dulcital fermentation—causes resistance to phagocytosis Erythrocyte agglutination—associated with uroepithelial

adherence

Drug resistance

Inherent resistance

Mutation and selection Resistance factor transfer

confer resistance to penicillins, cephalosporins, aminoglycosides, tetracyclines, chloramphenicol, sulfonamides, and trimethoprim.

Mycoplasmal organisms have also been associated with UTIs in dogs, but this type of infection is uncommon. Clinical signs of mycoplasmal cystitis may include hematuria, pollakiuria, stranguria, incontinence, polydipsia-polyuria, and fever; however, some dogs with positive urine culture results are asymptomatic. Whether mycoplasmas are primary urinary tract pathogens remains unclear.

### **HOST DEFENSE MECHANISMS**

The status of the host defense mechanisms appears to be the most important factor influencing the pathogenesis of UTI (Table 45-2). Normal voiding is an efficient natural defense



**TABLE 45-2** 

Host Defense Mechanisms and Abnormalities that May Lead to Complicated Urinary Tract Infections

HOST DEFENSES	ABNORMALITIES	
Normal Micturition		
Normal urine volume Normal voiding frequency Small residual urine volume	Urinary incontinence Urine outflow tract obstruction Incomplete bladder emptying	
Anatomic Structures		
Urethral high-pressure zone Urethral contraction and peristalsis Urethral length Vesicoureteral valvelike junction Ureteral contractions and peristalsis	Urethral anomalies Urethrostomy surgery Ectopic ureter Urachal diverticula Vesicoureteral reflux Indwelling urinary catheter Urinary incontinence Vaginal stricture Ureteral dilatation or hydroureter	
Mucosal Defense Barriers		
Antibody and muco- protein production Nonpathogenic flora colonization	Mucosal trauma Urolithiasis Catheterization Immunoglobulin A deficiency Neoplasia Cyclophosphamide-induced damage	
Antimicrobial Properties of	f Urine	
Hyperosmolality High urea concentration Acidic pH	Decreased urine concentration Glucosuria	
Systemic Immunocompeter	nce	
Cell-mediated immunity?	Immunosuppressive drug therapy	
Humoral immunity	Hyperadrenocorticism Diabetes melitus Chronic kidney disease Neoplasia	

mechanism against UTI. The mechanical washout that occurs as a result of complete voiding is responsible for removing more than 95% of nonadherent bacteria that gain entrance into the urinary bladder. Washout is enhanced by increased urine production and frequency of voiding. Disorders that decrease the frequency of voiding or the volume of voided urine or that result in an increased urine residual volume may predispose animals to the development of UTIs. The normal urine residual volume for dogs and cats is less than 0.2 to 0.4 ml/kg.

Bacteria are normally present in increasing numbers from the midurethra to the distal urethra, but these organisms seldom cause UTIs in normal dogs. The high-pressure zone in the midurethra and the spontaneous urethral contractions help prevent the ascension of bacteria. Differences in epithelial morphology (decreased epithelial receptor sites) also help decrease the number of bacteria that can colonize the proximal and middle sections of the urethra. The length of the urethra and zinc-containing bacteriostatic/bactericidal prostatic secretions contribute to a lower incidence of UTIs in male dogs than in female dogs. In both genders the valvelike nature of the vesicoureteral junction confers protection against the ascension of bacteria to the kidneys.

The colonization of vulval and preputial luminal mucous membranes by nonpathogenic flora also serves to decrease colonization by uropathogens. Normal flora occupy most of the epithelial receptor sites, produce bacteriocins that interfere with uropathogen metabolism, and have a high affinity but low requirement for the essential nutrients needed by uropathogens. In addition, mucosal secretions help prevent the adherence of uropathogens to the epithelium; specifically, secretory immunoglobulins do so by coating pathogenic bacteria, and glycosaminoglycans by forming a protective barrier over the epithelial surface.

The antibacterial properties of urine constitute an important host defense mechanism against UTIs. Urine is frequently bacteriostatic and sometimes can be bactericidal, depending on its composition. The combination of a low pH and high concentrations of urea and weak organic acids in concentrated urine inhibits bacterial growth. The increased urine-concentrating ability of cats compared with dogs is thought to be one of the reasons that normal cats have so few bacterial UTIs. Dilute urine formed in animals with polydipsic-polyuric disorders has less antibacterial activity than hypersthenuric urine does. For example, the prevalence of bacterial UTI is higher in both dogs and cats with chronic kidney disease (CKD). Animals with CKD also often have decreased concentrations of antibiotic in their urine during treatment associated with decreased renal excretion of the drug.

# COMPLICATED VERSUS UNCOMPLICATED URINARY TRACT INFECTIONS

Uncomplicated UTIs occur in the absence of underlying structural or functional abnormalities in the host defense mechanisms. They are easier to treat than complicated UTIs and are usually cleared soon after appropriate antibiotic treatment is initiated. Complicated UTIs are associated with defects in the host defense mechanisms (i.e., interference with normal micturition, anatomic defects, damage to mucosal barriers, alterations in urine volume or composition, or systemic immunocompromise). It is usually not possible to eliminate the clinical and clinicopathologic signs of complicated UTIs with antibiotic treatment alone; signs either persist during antibiotic treatment or recur shortly after antibiotic withdrawal. Because of the relatively low prevalence of UTIs in male dogs compared with female dogs,

any UTI in a male dog should be considered a complicated infection.

Disorders of micturition are often complicated by UTI. Urine retention or incomplete voiding allows more time for bacteria to multiply within the urinary tract. Urine retention may also cause bladder wall distention that can compress intramural vessels and thereby decrease the number of WBCs and other antimicrobial factors that enter the bladder lumen. Conversely, urinary incontinence associated with decreased urethral sphincter tone may predispose the patient to an ascending UTI. Damage to mucosal barriers (e.g., transitional cell carcinoma [TCC]) may also result in the development of a complicated UTI depending on the extent of the lesion and whether uropathogens are concurrently introduced. Interestingly, bacterial inoculation of the urinary bladder in experimental animals usually fails to establish a UTI that lasts beyond 2 to 3 days, unless the uroepithelium is first damaged by a chemical or mechanical insult.

Whenever the urinary bladder is catheterized, bacteria are carried up the urethra to the bladder. If the catheter is inserted too far and damages the bladder mucosa, the chance of infection increases greatly. Anatomic defects may also allow the ascending migration of bacteria (e.g., indwelling urinary catheter, ectopic ureter) or may damage mucosal barriers (e.g., urolithiasis, neoplasia, urachal remnant, thickened bladder wall caused by chronic inflammation). In one study of 137 dogs cared for in an intensive care unit, indwelling urethral catheters were associated with UTI in 26 cases (19%); another similar study of 39 dogs demonstrated a UTI rate of 10%. Decreased urine volume may also be associated with a heightened risk for UTI because of decreased washout (although concentrated urine has greater antibacterial properties), and altered urine composition (glucosuria or the excretion of irritating substances such as cyclophosphamide metabolites that result in hematuria) can make the environment more receptive to bacterial growth. In addition to these local factors, systemic disorders, such as renal failure, hyperadrenocorticism, prolonged corticosteroid administration, neoplasia, and diabetes mellitus, can result in a complicated UTI. Potential mechanisms suggested to increase the risk of UTI in dogs with hyperadrenocorticism and/or diabetes mellitus include enhanced bacterial growth in urine caused by glucosuria or decreased urine concentration, decreased neutrophil chemotaxis associated with glucosuria, and decreased inflammatory response and/or urine retention (detrusor muscle weakness) associated with hypercortisolemia. UTI is also common in dogs with thoracolumbar (T-L) disk disease. In a recent study of 92 dogs that underwent surgery for T-L disk disease, 25 (27%) had UTI. Risk factors for UTI in this study included female gender, the inability to ambulate or voluntarily void, lack of perioperative cefazolin administration, and decreased body temperature (<35° C) during the anesthetic period.

### RELAPSES VERSUS REINFECTIONS

Recurrences of clinical and clinicopathologic signs of UTI can be classified into two categories: relapses and reinfec-

tions. Relapses are infections caused by the same species of bacteria; the clinical signs recur relatively shortly after antibiotic withdrawal. In these cases the previous antibacterial treatment has failed to eliminate the organism. Relapses may result from the use of an improper antibiotic or dosage, the emergence of drug-resistant pathogens, or failure to eliminate factors that alter normal host defense mechanisms and allow the bacteria to persist (e.g., bacteria inside a urolith). Relapsing UTIs are frequently associated with a greater antimicrobial resistance than that observed in the original infection. Relapses in male dogs may result from chronic prostatic infections. Because of the blood-prostate barrier, antibiotics must be lipid soluble and have an alkaline or neutral  $pK_a$  (e.g., fluoroquinolones, trimethoprim-sulfa, chloramphenicol, carbenicillin) in order to gain access to the prostate.

Recurrent UTIs may also result from reinfection. In this case the previous antibacterial treatment cleared the first infection, but the urinary tract subsequently became infected with another bacterium. In most cases the interval between reinfections is longer than the interval between relapses (>2-4 weeks). The occurrence of reinfections often indicates that the factors that alter normal host defense mechanisms have not been eliminated. Alternatively, reinfections may be iatrogenic and occur as a result of follow-up catheterization. Reinfections with less invasive bacteria (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter cloacae*) generally suggest that the host's immune system is compromised. Similarly, *Corynebacterium urealyticum* UTI in dogs and cats has been associated with preexisting urinary tract disorders (e.g., incontinence and urine retention).

### **Clinical Features**

Inflammation of the lower urinary tract often results in pollakiuria, stranguria or dysuria, and gross or microscopic hematuria. Urinalysis findings compatible with a lower UTI include bacteriuria, hematuria, pyuria, and increased numbers of transitional epithelial cells in the urine sediment. In addition, an increased urine protein concentration and alkaline urine may be observed. However, bacteria as well as other urine sediment abnormalities are not always observed during urine sediment examination in animals with a bacterial UTI, especially if the urine is hyposthenuric or isosthenuric. Ideally, urine bacterial cultures should be performed to confirm the presence and type of bacteria. Research has shown that the testing of canine urine with commercially available dipstick leukocyte esterase assays is not reliable, and the false-negative rate can exceed 10% in the absence of a urine sediment examination. Some urine dipsticks also have a nitrate pad to detect nitrate-reducing bacteria, but this test has also been shown to be inaccurate in dogs and cats.

Cystocentesis constitutes the best way to collect urine for urinalysis and bacterial culture because it prevents urine from being contaminated by bacteria inhabiting the distal urethra, prepuce, or vulva. If urine collected by catheterization, voiding, or bladder expression is cultured, it is important to quantify the number of organisms per milliliter to differentiate a true infection from contamination (see Table



BOX 45-2

Clinicopathologic Findings that Can Be Associated with Bacterial Pyelonephritis in Dogs and Cats

Fever, leukocytosis, renal pain

Cellular casts in urine sediment

Renal failure (i.e., azotemia, inability to concentrate urine, polydipsia-polyuria)

Excretory urogram and ultrasonographic abnormalities (i.e., renal pelvis dilation or asymmetric filling of diverticula, dilated ureters)

Bacteria in inflammatory lesions identified by renal histologic studies

Positive result from bacterial culture of ureteral urine obtained at cystoscopy (Stamey test)

Positive result from bacterial culture of urine obtained after bladder rinsing with sterile saline solution (Fairley test) Positive result from bacterial culture of fluid aspirated from the renal pelvis (pyelocentesis) under ultrasound guidance

41-1). Bacterial antibiotic sensitivity testing should be performed to guide the selection of antibiotic treatment and, in cases of recurrent UTI, help differentiate relapses from reinfections. It may be difficult to differentiate a lower UTI from upper urinary tract involvement (as well as prostatitis), but this should be attempted to prevent renal damage in dogs and cats with pyelonephritis, which requires long-term antibiotic treatment and close monitoring (Box 45-2). Animals with acute bacterial pyelonephritis or prostatitis may manifest nonspecific systemic signs of lethargy, depression, anorexia, fever, and leukocytosis, which rarely occur in the setting lower UTIs. However, these systemic signs are frequently absent in animals with chronic pyelonephritis or prostatitis. Bilateral pyelonephritis may result in renal failure and subsequent azotemia and the loss of urineconcentrating ability. Cylindruria, especially WBC cellular casts, indicates the presence of renal disease and, if coupled with a significant bacteriuria, is highly suggestive of bacterial pyelonephritis. Several tests have been developed to differentiate upper and lower UTIs in people (see Box 45-2); however, these tests are difficult to perform and have not always proved reliable in veterinary medicine.

### **Treatment**

It is important to try to identify those animals with potentially treatable immune system defects or disorders (e.g., diabetes mellitus, hyperadrenocorticism, chronic renal failure, urolithiasis, urachal remnants, excessive perivulvar skin folds or pyoderma, incontinence) that predispose to the development of UTIs. Therefore a complete physical examination should be performed in all animals with signs of a UTI. Similarly, urinalysis and culture should be performed in all dogs and cats with suspected immune system defects. Although antibiotic treatment is the cornerstone of management, the status of host defense mechanisms is thought to be the single most important determinant of the outcome of

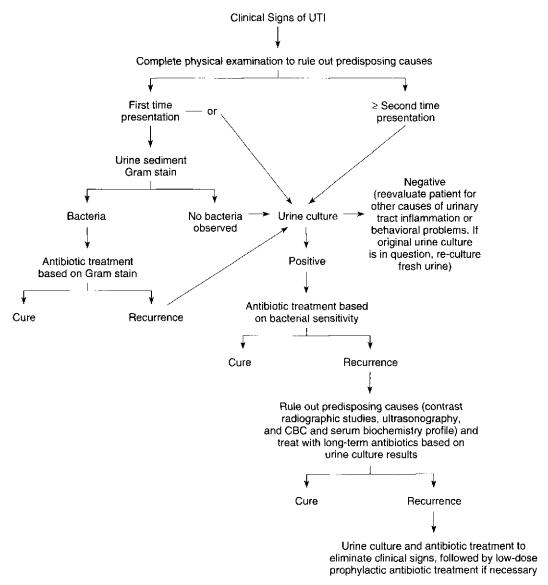


FIG 45-1
Flow diagram for management of urinary tract infections.

treatment for a UTI. Antibiotic treatment should control the pathogenic bacterial growth for enough time to allow host defense mechanisms to prevent colonization of the urinary tract without the need for further antibiotic administration. Although it is advisable to evaluate the bacterial sensitivity to antimicrobial drugs, the treatment of acute, uncomplicated UTIs is often dictated by economic and time considerations. If bacterial sensitivity results are not available, the antibiotic should be chosen on the basis of bacterial identification or the Gram's staining characteristics of the bacteria (Fig. 45-1). Clinical experience at several veterinary teaching hospitals has shown that intelligent guesses can be made regarding bacterial susceptibility to antibiotics. In the absence of bacterial sensitivity testing, the following are the drugs of choice for the treatment of infection with the bacteria listed: E. coli, trimethoprim-sulfa or enrofloxacin; Proteus, amoxicillin; Staphylococcus, amoxicillin; Streptococcus spp., amoxicillin; Enterobacter spp., trimethoprim-sulfa or enrofloxacin; Klebsiella spp., first-generation cephalosporins or enrofloxacin; and Pseudomonas spp., tetracycline (Table 45-3). It should be noted, however, that it is often difficult to predict the sensitivity of gram-negative enteric bacteria. If the identity of the bacteria is unknown, treatment should be determined on the basis of the Gram's staining characteristics (i.e., ampicillin, amoxicillin, or amoxicillin-clavulanic acid for gram-positive bacteria and trimethoprim-sulfa or enrofloxacin for gram-negative bacteria).

The steps to follow in the management of a UTI are given in Box 45-3, and a flow diagram is shown in Fig. 45-1. The duration of therapy for a lower UTI must be individualized and should be based on the cessation of clinical signs and elimination of the abnormal urine sediment as well as negative urine culture results. In general, uncomplicated lower UTIs should be treated for 2 weeks, whereas complicated



### **TABLE 45-3**

Antimicrobial Agents to Which More than 90% of Urinary Isolates Are Susceptible In Vitro at Concentrations Less than One Fourth of the Expected Urinary Concentration

ORGANISM	ANTIMICROBIAL AGENTS
F (++	The Market Mark
E. coli*	Trimethoprim-sulfa
	Fluoroquinolone
<b>.</b>	Amoxicillin-clavulanic acid
Coagulase-positive	Amoxicillin
Staphylococcus spp.	Chloramphenicol
	Trimethoprim-sulfa
	Cephalosporins (first generation)
Proteus mirabilis	Amoxicillin
	Fluoroquinolone
	Cephalosporins (first, second,
	third generations)
	Amoxicillin-clavulanic acid
Klebsiella	Cephalosporins (first, second,
pneumoniae*	third generations)
	Fluoroquinolone
	Amoxicillin-clavulanic acid
	Trimethoprim-sulfa
Streptococcus spp.	Amoxicillin
	Amoxicillin–clavulanic acid
	Chloramphenical
	Cephalosporins (first, second,
	third generations)
Pseudomonas	Tetracycline
aeruginosa	Fluoroquinolone
· ·	Carbenicillin
Enterobacter spp.*	Trimethoprim-sulfa
	Fluoroquinolone
Enterococcus spp.	Fluoroquinolone
1 1	Trimethoprim-sulfa
	Chloramphenicol
	Tetracyline
	·-··/·····-

<sup>\*</sup>These bacteria are capable of major changes in their susceptibility to antibiotics and are therefore less predictable.

UTIs should be treated for a minimum of 4 weeks. Proper selection of antibiotic therapy can be verified after 3 to 5 days of therapy by determining whether the urine is sterile. The urine sediment, however, may still be abnormal at this time.

Reasons for a poor therapeutic response are listed in Box 45-4. Urine culture and sensitivity testing should always be done in animals with recurrent UTIs. In addition, attempts should be intensified to identify defects in the host's immune system. Double contrast—enhanced cystography and ultrasonography may be used to identify anatomic abnormalities, mucosal lesions of the bladder, or urolithiasis. In intact male dogs semen and prostatic wash cytologic and culture studies as well as ultrasonography should be done to rule out or identify bacterial prostatitis. Excretory urographic, ultraso-



### BOX 45-3

Ideal Steps to Follow in the Management of Urinary Tract Infections in Dogs and Cats

Diagnosis should be determined on the basis of history; urine sediment; and, ideally, urine culture and sensitivity findings.

Select an antimicrobial agent.

Reculture urine in 3 to 5 days to ascertain effectiveness of selected antimicrobial agent.

Examine urine sediment 3 to 4 days before discontinuing antibiotic treatment.

Repeat urinalysis and culture 10 to 14 days after cessation of antibiotic therapy.

Patients with recurrent urinary tract infections should undergo contrast-enhanced radiography and/or ultrasonography, a complete blood count, and serum biochemistry profile to determine whether they have underlying pre-disposing factors.

It may be necessary to treat frequent reinfections with prophylactic doses of antibiotics after the initial inflammation has been cleared up in response to standard-dose antibiotic treatment.



### BOX 45-4

Reasons for Poor Therapeutic Response in Dogs and Cats with Urinary Tract Infections

Use of ineffective drugs or ineffective duration of therapy Failure of owner to administer prescribed dose at proper intervals

Gastrointestinal tract disease or concurrent oral intake of food and drug, resulting in decreased drug absorption Impaired action of drugs, either because bacteria are not multiplying or because they are sequestered in an inaccessible site (e.g., prostate or uroliths)

Failure to recognize and eliminate predisposing causes
Presence of mixed bacterial infections in which only one of
the pathogens is eradicated by antimicrobial therapy
latrogenic reinfection caused by catheterization
Development of drug resistance in bacteria

nographic, and renal biopsy findings may confirm the presence of pyelonephritis; however, results of these studies may be normal in dogs and cats with chronic pyelonephritis. In patients with moderate to marked pyeloectasia, ultrasound-guided pyelocentesis can be used to obtain samples for cytology and culture. Finally, the possibility of otherwise asymptomatic hyperadrenocorticism causing the recurrent UTIs should be considered, especially in animals with infections associated with low numbers of WBCs and RBCs in the urine sediment. Long-term (4 to 6 weeks) antibiotic treatment is required for patients with complicated UTIs, and careful follow-up examinations should be performed in such animals (see Box 45-3). When antibiotic treatment is used

for this period of time, the adverse effects of long-term antibiotic therapy should also be considered. Keratoconjunctivitis sicca and folate deficiency anemia may occur in association with long-term use of trimethoprim-sulfa (although they are rare), and nephrotoxicity is always a concern in animals receiving aminoglycosides, even for a short time.

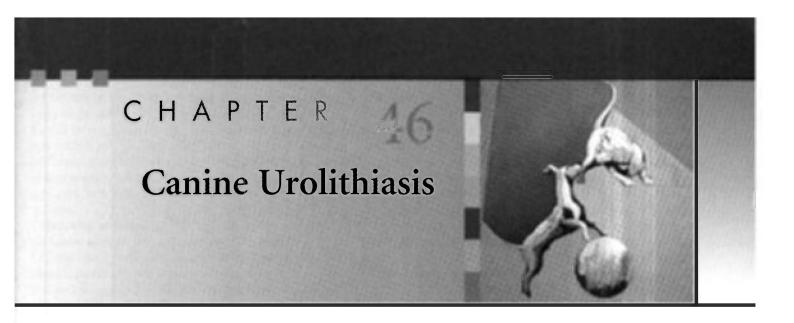
The prognosis for an animal with a complicated UTI, as opposed to an uncomplicated UTI, is always guarded. The single most important treatment for a complicated UTI is correction of the underlying defect in the host defense mechanisms. If predisposing factors cannot be identified or eliminated, relapses and reinfections are common. Low-dose (one third to one half of the conventional daily dose) antimicrobial treatment administered at bedtime (after the last evening void) may be recommended for animals with frequent infections associated with host defense mechanism problems that cannot be cured. This allows the drug to be present in the bladder overnight, supplementing the animal's defense mechanisms. Penicillins are recommended for the treatment of recurrences caused by gram-positive bacteria, whereas trimethoprim-sulfa or enrofloxacin is recommended for the treatment of recurrences caused by gram-negative bacteria. It should be noted, however, that low-dose, longterm antibiotic treatment can predispose the animal to the development of a very resistant UTI.

Urinary acidification (ammonium chloride) has been advocated as adjunctive therapy for lower UTIs because acidic urine provides a less favorable environment for bacterial growth. However, the antimicrobial activity of acidic urine is inferior to that of antibiotics and should not be expected to eradicate infection; ammonium chloride should be used only in conjunction with other modes of therapy. Urinary acidification may also be an effective adjunctive therapy to adjust the urine pH and thereby optimize the efficacy of certain antibiotics (penicillin, ampicillin, carbenicillin, tetracycline, nitrofurantoin). Ammonium chloride (60 to 100 mg/kg) should be given orally twice daily to maintain a urine pH of less than 6.5. The use of ammonium chloride is not without risk, however, especially in male dogs, because oxalate, silicate, urate, and cystine are all less soluble in acidic urine and urolithiasis may result from excessive acidification. In addition, urinary acidification would be contraindicated in dogs with liver or kidney disease. Urinary antiseptics have also been advocated as adjunctive therapy in the control or prophylaxis of lower UTIs. Although they are less effective than specific antimicrobial therapy in eradicating infections, they are probably more effective than urinary acidifiers. Methenamine mandelate is a cyclic hydrocarbon and is the most commonly used urinary tract antiseptic. The dose for dogs is 10 mg/kg, administered orally every 6 hours. In an acidic environment (pH < 6), methenamine hydrolyzes to form formaldehyde. It should be used in conjunction with ammonium chloride to enhance its effectiveness. Methylene blue (tetramethylthionine chloride) is a weak urinary antiseptic agent that used to be common in combination products designed to treat lower urinary tract inflammation in people. These products should not be used in cats, however, because methylene blue has the potential to cause Heinz bodies and hemolytic anemia. Similarly, phenazopyridine, a urinary tract analgesic, should not be used in cats.

Cranberry juice extracts, glycosaminoglycans, and vaccines directed against bacterial fimbria are additional adjunctive treatments that can decrease bacterial adherence to uroepithelium in other species but require further evaluation in the dog before clinical recommendations can be made.

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### CHAPTER OUTLINE

GENERAL CONSIDERATIONS

Etiology and Pathogenesis

Clinical features and diagnosis

Treatment

MONITORING THE PATIENT WITH UROLITHIASIS

### **GENERAL CONSIDERATIONS**

Canine urine is a complex solution in which salts (e.g., calcium oxalate, magnesium ammonium phosphate) can remain in solution under conditions of supersaturation. However, supersaturated urine has a potential energy of precipitation, or the tendency to form solids from the dissolved salts. Crystalluria is a consequence of urine supersaturation, and uroliths may form if crystals aggregate and are not excreted. Uroliths may damage the uroepithelium and result in urinary tract inflammation (hematuria, pollakiuria, dysuria-stranguria). They may also predispose the animal to the development of a bacterial urinary tract infection (UTI). If uroliths lodge in the ureters or urethra, urine flow may be obstructed.

Most uroliths in dogs are found in the bladder or urethra; only about 5% are located in the kidneys or ureters. Uroliths are usually named according to their mineral content. Recent data collected at the College of Veterinary Medicine of the University of Minnesota have shown that approximately 38% of canine uroliths are struvite (magnesium ammonium phosphate), 42% are calcium oxalate, 5% are urate, 1% are silicate, 1% are cystine, and 14% are mixed or compound uroliths (i.e., the urolith contains less than 70% of any one mineral type). Crystalline aggregates constitute approximately 95% of the urolith weight, and an organic matrix composed of protein and mucoprotein complexes may constitute as much as 5%. Factors associated with particular types of uroliths are summarized in Table 46-1.

### **Etiology and Pathogenesis**

Conditions that contribute to the crystallization of salts and the formation of uroliths include a sufficiently high concentration of salts in the urine, adequate time in the urinary tract (urinary retention of salts and crystals), a urine pH favorable for salts to crystallize, a nucleation center or nidus on which crystallization can occur, and decreased concentrations of crystallization inhibitors in the urine. The combination of a high dietary intake of minerals and protein and the ability of dogs to produce relatively highly concentrated urine contributes to the supersaturation of urine with salts. In some cases decreased tubular resorption (e.g., calcium, cystine, uric acid) or an increased production secondary to bacterial infection (e.g., ammonium and phosphate ions) also contributes to this supersaturation.

Several theories exist concerning the pathogenesis of uroliths. In the precipitation-crystallization theory, the supersaturation of urine with salts is thought to be the primary factor responsible for initiating nidus formation and sustaining the growth of the urolith. Normal canine urine is supersaturated with several salts. However, the greater the concentration of salts in urine and the less often voiding occurs (e.g., decreased water intake), the greater the chance of urolith formation. Supersaturated urine has a potential energy of precipitation, or a driving force that favors crystal formation. The greater the magnitude of the supersaturation, the greater the potential for crystallization to occur. Conversely, undersaturated solutions have a potential energy of dissolution, such that previously formed crystals dissolve at a rate proportional to the degree of undersaturation.

In other theories of urolith formation, it is thought that substances in urine may promote or inhibit crystal formation. For example, in the matrix nucleation theory an organic matrix substance in urine is thought to promote initial nidus formation. This matrix substance may be albumin, globulin, Tamm-Horsfall mucoprotein, or an immunologically unique hydroxyproline-deficient protein called *matrix substance A*. The proteinaceous matrix substance may promote crystallization by providing a surface where crystallization can occur and by binding crystals together, which may increase their urinary retention. According to another theory, the crystallization inhibitor theory, the absence of a critical inhibitor of crystal formation is considered to be the primary factor that allows initial nidus formation. Examples of

# TABLE 46-1 Factors that Help Predict Urolith Composition

UROLITH TYPE	RADIOGRAPHIC DENSITY (1.0-3.0 scale)	USUAL URINE pH	URINARY TRACT	GENDER PREDISPOSITION	COMMONLY AFFECTED BREEDS	COMMONLY AFFECTED AGES (yr)	CLINICOPATHOLOGIC ABNORMALITIES
Magnesium ammonium phosphate (struvite)	2.5	Neutral to alkaline	Very common, especially urease- producing bacteria (e.g., Staphylococcus, Proteus)	Female (>80%)	Miniature Schnauzers, Bichon Frises, Cocker Spaniels, Miniature Poodles	1-8	Usually none
Calcium oxalate	3.0	Acidic to neutral	Rare	Male (>70%)	Miniature Schnauzers, Miniature Poodles, Yorkshire Terriers, Lhasa Apsos, Bichon Frises, Shih Tzus, Cairn Terriers	5-12	Occasional hypercalcemia
Urate	1.0	Acidic to neutral	Uncommon	Male (>90%)	Dalmatians, English Bulldogs, Miniature Schnauzers (PSS), Yorkshire Terriers (PSS)	1-4	Decreased serum urea, nitrogen, and albumin concentrations and abnormal preprandial and postprandial bile acid concentrations in dogs with PSS
Cystine	1.5	Acidic	Rare	Male (>95%)	Dachshunds, Basset Hounds, English Bulldogs, Yorkshire Terriers, Irish Terriers, Rottweilers, Chihauhaus, Mastiffs, Tibetan Spaniels	1 <i>-7</i>	Usually none
Silicate	2.5	Acidic to neutral	Uncommon	Male (>95%)	German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, Old English Sheepdogs	4-9	Usually none

PSS, Portosystemic shunt.

crystallization inhibitors are citrates, glycosaminoglycans, and pyrophosphates. Decreased concentrations of these substances in urine may facilitate spontaneous crystallization and urolith growth. The extent to which promoters and inhibitors of crystallization are involved in urolith formation in dogs is unknown. In all cases, however, supersaturation of the urine with urolith constituents is essential for uroliths to form.

Struvite uroliths. Struvite or magnesium ammonium phosphate uroliths are common uroliths in dogs (Fig. 46-1). Uroliths that predominantly consist of struvite may also contain a small amount of calcium phosphate (hydroxyapatite) or calcium carbonate. Because most canine diets are rich in minerals and protein, canine urine frequently becomes supersaturated with magnesium, ammonium, and phosphate; however, a UTI is an important factor predisposing to the formation of struvite uroliths in dogs and *Staphylococcus* and *Proteus* are commonly associated pathogens. These bacteria contain urease and are capable of splitting urea into ammonia and carbon dioxide. Hydroxyl and ammonium ions are formed by the hydrolysis of ammonia, which decreases hydrogen ion concentrations in urine, resulting in an alkaline urine and decreased struvite solubility. The



**FIG 46-1 A,** Typical appearance of struvite stones, although struvite stones may also be jack shaped **(B)**. **(B** courtesy Dr. Howard Seim, Colorado State University.)

hydrolysis of urea increases the urine concentrations of ammonium and phosphate (a result of the increased dissociation of phosphorus) ions, which augments urine supersaturation. High urine ammonia concentrations may also damage glycosaminoglycans that prevent bacteria from adhering to the urinary mucosa. Bacterial cystitis also increases the amount of organic debris available as a crystallization surface. Because of their high association with UTIs, struvite uroliths are more common in female dogs (80% to 97% of uroliths in female dogs are struvite). Uroliths in dogs younger than 1 year of age are usually struvite and are also frequently associated with a UTI.

The factors involved in the pathogenesis of struvite uroliths in sterile urine are not known; however, the struvite uroliths that form in cats usually do so in the absence of a UTI. A greater urine-concentrating ability, and therefore a greater degree of urine supersaturation, may be partially responsible for causing uroliths to form in cats and in those dogs without UTIs. In addition, a consistently high urine pH in the absence of a UTI (potentially caused by drugs, diet, or renal tubular disorders) may facilitate struvite urolith formation.

Although struvite uroliths may occur in any breed, those most commonly affected include Miniature Schnauzers, Miniature Poodles, Bichon Frises, and Cocker Spaniels. The high prevalence of struvite uroliths in Cocker Spaniels has led to the suggestion that there is a familial predisposition in this breed (see Table 46-1). Uroliths larger than 1 cm in any dimension are likely to be struvite. In addition, struvite uroliths found in the urinary bladder are most likely to be smooth, blunt-edged or faceted, or pyramidal.

Calcium oxalate uroliths. Calcium oxalate uroliths in dogs are often the monohydrate (whewellite) form (Fig. 46-2, A; see also Fig. 41-3) rather than the dihydrate (weddellite) form (see Figs. 41-4 and 46-2, B). The factors involved in the pathogenesis of calcium oxalate urolithiasis in dogs are not completely understood but frequently involve increased concentrations of calcium in the urine. Hypercalciuria probably occurs most commonly in dogs postprandially and is associated with increased absorption of calcium from the gut. Another potential cause of hypercalciuria is the defective tubular resorption of calcium. Hypercalciuria may also occur secondary to overt hypercalcemia (e.g., that resulting from primary hyperparathyroidism, neoplasia, or vitamin D intoxication); however, this is thought to be an infrequent cause of calcium oxalate uroliths. Treatment with certain drugs (e.g., glucocorticoids, furosemide) as well as dietary supplementation with calcium or sodium chloride may also result in hypercalciuria. An association between hyperadrenocorticism and the development of calcium-containing uroliths has also been identified in dogs. Finally, decreased urine concentrations of glycosaminoglycans, Tamm-Horsfall protein, osteopontine, and/or citrate, which are calcium oxalate crystallization inhibitors, or defective urinary nephrocalcin or increased dietary intake of oxalate (e.g., vegetables, grass, vitamin C) may play a role in the pathogenesis of calcium oxalate urolithiasis in some dogs. The overall preva-

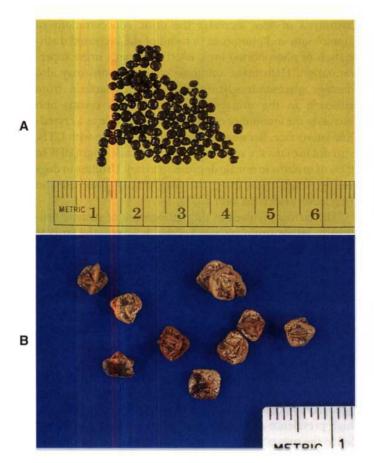


FIG 46-2
Typical appearance of monohydrate calcium oxalate stones
(A) and dihydrate calcium oxalate stones (B).

lence of calcium oxalate uroliths in dogs has increased significantly over the past 10 years and may be related to the increased use of urine-acidifying diets or other unidentified environmental factors.

Approximately 70% of calcium oxalate uroliths are found in male dogs, and Miniature and Standard Schnauzers, Miniature Poodles, Yorkshire Terriers, Lhasa Apsos, Bichon Frises, and Shih Tzus are the breeds commonly affected. Obesity also appears to increase the risk of calcium oxalate urolithiasis. The increased prevalence in male dogs may be related to an increase in the hepatic production of oxalate mediated by testosterone. Conversely, estrogens in female dogs may increase the urinary excretion of citrate. Calcium oxalate uroliths frequently occur in older dogs (mean age: 8 to 12 years), and a concurrent UTI appears to be rare. Calcium oxalate solubility is increased in urine with a pH above 6.5, whereas a urine pH of less than 6.5 favors calcium oxalate crystal formation.

**Urate uroliths.** Most urate uroliths are composed of ammonium acid urate; 100% uric acid and sodium urate uroliths are relatively rare (Fig. 46-3). Uric acid is derived from the metabolic degradation of endogenous purine ribonucleotides and dietary nucleic acids. It is hypothesized that the hepatic transport of uric acid is defective in Dalmatians and some English Bulldogs because uric acid conversion to



**FIG 46-3** Appearance of ammonium urate stones from two different dogs.

allantoin has been found to be decreased in them, even though hepatocyte uricase activities are often adequate. The decreased production of allantoin seen in these breeds results in the increased urinary excretion of uric acid. Normally, allantoin, which is produced through the oxidation of uric acid by uricase, is the major metabolite generated during purine metabolism. In comparison with uric acid, allantoin is quite soluble in urine.

In addition to a decreased hepatic metabolism of uric acid, the proximal tubular resorption of uric acid appears to be decreased in Dalmatians. This increases the uric acid and sodium urate (the salt of uric acid) concentrations in urine. Although urinary uric acid excretion in Dalmatians is approximately 10 times that of other dogs, urate stones form in only a small percentage. For unknown reasons, male Dalmatians are at greater risk of having urate stones than are female Dalmatians. In one published study the male: female ratio for urate stone–forming Dalmatians was reported to be 16.4:1. Approximately 60% of urate uroliths occur in Dalmatians, and, conversely, approximately 75% of the uroliths in Dalmatians are urate uroliths. In addition to Dalmatians, English Bulldogs have an increased incidence of urate uroliths.

Another possible cause of urate stone formation is a decreased glycosaminoglycan concentration in the urine.

Glycosaminoglycans in urine may combine with urate salts, resulting in an overall negative charge and reduced crystallization. High dietary protein is usually associated with an increase in the urinary excretion of both uric acid and ammonium ions. Ammonia, which is produced by renal tubular cells from glutamine, diffuses into the tubular lumen and serves as a buffer for secreted hydrogen ions, thereby forming ammonium ions. Ammonium ions are relatively lipid insoluble and therefore become trapped within the tubular fluid. Uric acid crystallization is facilitated in acidic urine, whereas an alkaline urine appears to favor ammonium urate crystallization. Ammonium acid urate stones may also form in any dog with hepatic insufficiency (e.g., hepatic cirrhosis, microvascular dysplasia, or portosystemic shunt [PSS]) as a result of increased renal excretion of ammonium urates. PSSs are common in Miniature Schnauzers, Yorkshire Terriers, and Pekingese dogs; therefore ammonium acid urate uroliths are more common in these breeds. UTIs, especially those with urease-producing bacteria, may facilitate ammonium acid urate crystallization by increasing urine ammonia concentrations. A UTI may also occur secondary to urolith-induced mucosal irritation.

Silicate uroliths. Silicate uroliths were first reported in the United States in 1976 in association with crystallographic analysis of uroliths. Silicate uroliths frequently, but not always, have a jack shape (Fig. 46-4), although not all jackstones are silicates (ammonium urate and struvite uroliths may also be jack shaped; see Fig. 46-1, B). The factors responsible for the pathogenesis of silicate uroliths are unknown, but their formation is probably related to the dietary intake of silicates, silicic acid, or magnesium silicate. There appears to be a link between the formation of silicate uroliths and the consumption of large amounts of corn gluten or soybean hulls, which can be high in silicates. Many of the reported silicate uroliths in the United States have occurred in male German Shepherd Dogs, Old English Sheepdogs, and Golden and Labrador Retrievers. Most silicate uroliths are diagnosed in dogs 6 to 8 years of age. Alkaline urine appears to increase

silicate solubility, and secondary UTIs may occur as a result of mucosal irritation caused by these jack-shaped uroliths.

Cystine uroliths. Cystinuria, an inherited disorder of renal tubular transport, is thought to be the primary cause of cystine uroliths. The tubular resorptive defect involves cystine and, in some cases, other amino acids (tubular resorption of cysteine, the immediate precursor of cystine, glycine, ornithine, carnitine, arginine, and lysine, may also be decreased). Although the plasma cystine concentrations are normal in these dogs, the concentration of plasma methionine, a precursor of cystine, may be increased. Plasma cystine is freely filtered through the glomeruli and is actively resorbed by proximal tubular epithelial cells in normal dogs. Were it not for the relative insolubility of cystine in urine and the potential for uroliths to form, cystinuria would be of little consequence. Cystine is most soluble in alkaline solutions; therefore cystine stones usually form in acidic urine. Interestingly, cystine uroliths do not form in all dogs with cystinuria; therefore cystinuria is a predisposing, rather than a primary, causative factor. Cystine uroliths (Fig. 46-5) are most frequently observed in male dogs, and Dachshunds are the breed principally affected, but Basset Hounds, Tibetan Spaniels, English Bulldogs, Yorkshire Terriers, Irish Terriers, Chihuahuas, Mastiffs, and Rottweilers also appear to be at increased risk for cystine urolithiasis.

For unknown reasons, cystine uroliths usually do not form in young dogs; the average age at detection is 3 to 6 years. The prevalence of cystine urolithiasis in dogs in the United Kingdom has been reported to be much higher than that seen in dogs in the United States, probably reflecting the increased popularity of affected breeds in the United Kingdom. UTIs may occur secondarily; however, infection is not thought to play a primary role in the pathogenesis of cystine uroliths.

### **Clinical Features and Diagnosis**

The clinical features of urolithiasis depend on the number, type, and location of the stones in the urinary tract. Because



**FIG 46-4** Typical appearance of a silicate stone.



**FIG 46-5** Typical appearance of cystine stones.

most uroliths are located in the urinary bladder, clinical signs of cystitis (hematuria, pollakiuria, dysuria-stranguria) are frequently observed. Mucosal irritation is relatively severe in dogs with jack-shaped uroliths, as opposed to that seen in dogs with solitary, smooth stones. Incomplete voiding (i.e., urine retention), mucosal hyperplasia leading to polyp formation, and sequestration of bacteria within the stone are additional complications associated with urolithiasis. In male dogs smaller uroliths may pass into the urethra, causing partial or complete obstruction with signs of bladder distention, dysuria-stranguria, and postrenal azotemia (depression, anorexia, vomiting). Uroliths frequently lodge in the male urethra at the caudal aspect of the os penis (Fig. 46-6). Occasionally, the urinary bladder or urethra may rupture and result in an abdominal effusion or subcutaneous perineal fluid accumulation and postrenal azotemia. Animals

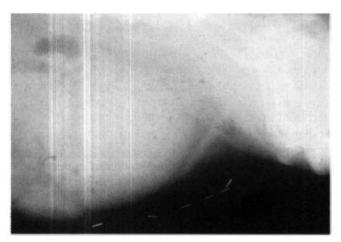
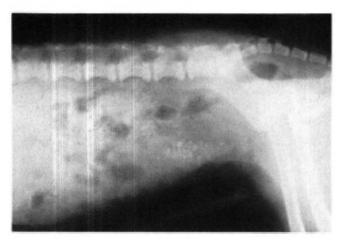


FIG 46-6
Radiograph of a male dog with an opaque urethral calculus at the caudal aspect of the os penis. Note the distended bladder associated with the obstructive uropathy and the staples from a previous cystotomy for urolith removal.



**FIG 46-7**Typical appearance of radiopaque cystouroliths on plain film radiographs. (Courtesy Dr. Philip Steyn, Colorado State University, Fort Collins, Colo.)

with unilateral renal uroliths may be asymptomatic, or they may have hematuria and chronic pyelonephritis. Frequently, chronic kidney disease develops in animals with bilateral renal uroliths, especially if pyelonephritis is also present. Dogs with ureteral uroliths may also be asymptomatic, or they may have hematuria and abdominal pain. Unilateral obstruction of a ureter often results in unilateral hydrone-phrosis without evidence of decreased renal function.

Canine urolithiasis is usually diagnosed on the basis of a combination of historical, physical examination, and radiographic or ultrasonographic findings (Fig. 46-7). In male dogs with dysuria and stranguria caused by urethral stones, attempted passage of a urinary catheter will often be met with a "gritty feeling" of resistance. Regardless of the ease of catheter passage, the diagnosis can usually be confirmed with retrograde positive contrast-enhanced urethrography. In some cases cystouroliths can be detected during abdominal palpation in dogs with signs of cystitis. Plain film radiographs will usually confirm the presence of cystouroliths unless the stones are radiolucent or very small. Doublecontrast-enhanced cystography is a more sensitive diagnostic tool for detecting radiolucent cystouroliths. Finally, ultrasonography can be used to visualize radioopaque or radiolucent uroliths and is the imaging method of choice for diagnosing renoliths and hydronephrosis-hydroureter that can be associated with renoliths.

### **Treatment**

General principles for the treatment of urolithiasis include the relief of any urethral obstruction and decompression of the bladder, if necessary. This can usually be accomplished by the passage of a small-bore catheter, cystocentesis, or dislodgment of the urethral calculi by retrograde hydropulsion. Only rarely will an emergency urethrotomy be necessary. Fluid therapy should be initiated to restore water and electrolyte balance if postrenal azotemia exists. Hyperkalemia is a potentially life-threatening electrolyte disturbance that may occur in association with postrenal azotemia caused by urethral obstruction or rupture of the urinary bladder or urethra. The serum potassium concentration as well as the blood urea nitrogen and creatinine concentrations should be measured in patients with a suspected obstruction. Alternatively, bradycardia and electrocardiographic findings of flattened P waves, a prolonged PR interval, widened QRS complexes, and tall or spiked T waves are suggestive of hyperkalemia and indicate the need for aggressive treatment to lower the serum potassium concentration. Hyperkalemia should be promptly treated according to the regimen outlined in Box 46-1.

The medical dissolution of struvite, urate, and cystine uroliths has been shown to be effective (Table 46-2); however, the choice between the surgical removal of uroliths and medical dissolution is not always clear. Disadvantages of surgery include the need for anesthesia, the invasiveness of the procedure (potential surgical complications), the possibility of incomplete removal of uroliths, and the persistence of underlying causes. Inasmuch as the underlying cause is



BOX 46-1

Electrocardiographic Findings and Treatment Recommendations for Dogs and Cats with Hyperkalemia

### **ECG Findings**

- 1. Bradycardia
- 2. Flattened waves
- 3. Prolonged PR interval
- 4. Widened QRS complexes
- 5. Tall or spiked T waves
- 6. Arrhythmias

### **Treatment Recommendations**

- 1. Fluid therapy with 0.9% saline solution
- Slow IV bolus of regular insulin (0.25-0.5 U/kg), followed by 50% dextrose (4 ml/U of administered insulin), or
- 3. Slow IV bolus of sodium bicarbonate (1-2 mEq/kg), or
- Slow IV balus of 10% calcium gluconate (0.5-1.0 ml/kg while manitoring the ECG)

ECG, Electrocardiogram; IV, intravenous.

usually not eliminated, surgery typically does not lead to a decrease in the rate of urolith recurrence. Advantages of surgery include the fact that the urolith type can be definitively diagnosed, any concurrent or predisposing anatomic abnormalities (e.g., urachal remnants, urinary bladder polyps) can be corrected, and urinary bladder mucosal samples can be obtained for bacterial culture if the urine yields no growth on culture.

Medical treatment decreases the concentration of calculogenic salts in the urine, increases salt solubility in urine, and increases urine volume, which produces urine with a lower concentration of calculogenic salts. The major disadvantage of the medical treatment of urolithiasis is that considerable owner compliance is required for several weeks to months. The cost of medical dissolution is comparable to the cost of surgery because multiple urinalyses, bacterial cultures, and frequent radiographs are required for follow-up. Animals with urolith-induced obstructive uropathy cannot be treated medically, and some uroliths (calcium oxalate, calcium phosphate, silicate, and mixed-composition uroliths) do not respond to medical dissolution. In addition to the medical dissolution of uroliths, voiding urohydropropulsion or catheter urolith retrieval can be used to remove cystouroliths nonsurgically in some animals (Box 46-2; see also Lulich et al., 1992, 1993, for detailed instructions). Lithotripsy, available at some referral centers, has also been used successfully to treat nephroliths and, less commonly, ureteroliths in dogs.

General preventive measures to be taken in addition to the surgical or medical management of uroliths include the induction of diuresis and the eradication of UTIs. Diuresis is important because it lowers the urine specific gravity and the urinary concentration of calculogenic salts. Feeding canned food will help increase water intake. In general, the maintenance of a urine specific gravity of less than 1.020 is ideal, and dogs should be allowed frequent opportunities to void. The urine sediment and pH should be monitored routinely, and UTIs should be treated promptly on the basis of bacterial culture and sensitivity results (see specific instructions in discussion of each type of urolith).



**TABLE 46-2** 

Treatment and Prevention of Urolithiasis in Dogs

UROLITH TYPE	TREATMENT OPTIONS	PREVENTION	
Struvite	Surgical removal or dissolution:	Hill's c/d diet	
	Hill's s/d diet	Monitor urine pH and urine sediment,	
	Control infection	and treat any infections quickly	
	Urease inhibitor?	and appropriately	
	Keep urine pH < 6.5, BUN < 10 mg/dl, and urine specific gravity <1.020	, ,	
Calcium oxalate	Surgical removal	Hill's u/d diet	
Urate	Surgical removal or dissolution:	Potassium citrate?	
	Hill's u/d diet	Hill's u/d diet	
	Allopurinol (7-10 mg/kg q8-24h PO) Control infection	Allopurinol if necessary	
Silicate	Surgical removal	Hill's v/d diet	
		Prevent consumption of dirt and grass	
Cystine	Surgical removal or dissolution:	Hill's u/d diet	
,	Hill's u/d diet	Thiol-containing drugs if necessary	
	N-(2-mercaptopropionyl)-glycine (15-20 mg/kg q/2h PO)	3 · · · 9 · · · · · · · · · · · · · · ·	



### Guidelines for Urohydropropulsion

- Assess uralith size and shape in relation to animal size: Uraliths must be smaller than the smallest urethral diameter.
  - Smooth uraliths will pass more readily than those with irregular surfaces.
- Sedation facilitates animal positioning. Consider analgesia and muscle relaxation.
- 3. General anesthesia may also be used.
- Moderately distend the bladder with sterile saline solution administered through a urethral catheter (4-6 ml/ kg of body weight), and assess bladder size by abdominal palpation.
- 5. Remove urethral catheter.
- Position the animal so that its vertebral column is vertical.
- Gently agitate the bladder using abdominal palpation to move uroliths into the trigone region.
- Apply steady digital pressure to the bladder to express urine and uroliths.
- 9. Steps 4 through 8 can be repeated as necessary.
- Assess complete urolith removal with follow-up radiographs or double-contrast-enhanced cystograms.

Struvite uroliths. Struvite uroliths can usually be dissolved by feeding the animal a struvite dissolution diet (e.g., Hill's Canine Prescription Diet s/d and Royal Canin canine URINARY SO). It takes an average of 8 to 10 weeks (range: 2 weeks to 7 months) for struvite uroliths to be dissolved in this way. The rate at which uroliths dissolve is proportional to the surface area of the urolith exposed to the undersaturated urine and the presence or absence of a UTI (sterile struvite uroliths will dissolve more rapidly than those associated with a UTI). These diets should not be fed routinely as a maintenance diet and should not be used in pregnant, lactating, or growing animals or after surgery because wound healing may be compromised as a result of the restricted protein in the diet. In addition, because of its high salt content, struvite dissolution diets should not be fed to dogs with congestive heart failure, hypertension, or nephrotic syndrome. In Miniature Schnauzers, the high fat content of the s/d diet may exacerbate any lipid abnormalities and increase the risk of pancreatitis; in this case Hill's Prescription Diet w/d may be used. The dissolution diet should be fed for a minimum of 30 days after the calculi are no longer visible radiographically. It should be noted that these diets will not dissolve nonstruvite uroliths and will not be effective if a UTI persists or if the animal is fed anything in addition to the dissolution diet. Lack of owner compliance with the dietary recommendations (i.e., instructions to feed the dissolution diet only) is indicated if the serum urea nitrogen concentrations remain greater than 10 mg/dl after the diet has been initiated.

In addition to decreasing the concentration of crystalloids in the urine, the elimination of any bacterial UTI is an essential part of the medical treatment of struvite urolithiasis. If infection is present at the start of treatment, antibiotics should be continued throughout the course of the medical dissolution treatment to destroy viable bacteria that may be liberated from the urolith as it dissolves. Antibiotics should be selected on the basis of urine culture and sensitivity findings; in cases of severe or persistent UTIs caused by ureaseproducing bacteria, the urease inhibitor acetohydroxamic acid (Lithostat; Mission Pharmacal, San Antonio, Texas) may be added to the treatment, but it is rarely needed. At a dose of 12.5 mg/kg, administered orally q12h, it may help dissolve struvite uroliths that are resistant to antibiotic and dietary treatment. Adjunctive treatment with urinary acidifiers in conjunction with the struvite dissolution diets is usually not recommended. The most common causes of alkaline urine during diet treatment are a persistent bacterial infection and lack of dietary compliance. The medical treatment of sterile struvite uroliths is the same as that described in previous paragraphs, except that antibiotics are not necessary.

Measures to prevent the recurrence of struvite uroliths include preventing and controlling UTIs, maintaining an acidic urine, and decreasing the dietary intake of calculogenic salts. Hill's Canine Prescription Diet c/d is a good maintenance diet to prevent sterile struvite urolith recurrence because the protein, magnesium, calcium, and phosphorous content is only moderately restricted and it produces an acidic urine. In dogs with recurrent UTIs, predisposing abnormalities (e.g., urachal remnant, urinary bladder polyp) should be identified or ruled out with double-contrastenhanced cystography or ultrasonography. Otherwise, silent hyperadrenocorticism may also result in recurrent UTI (see Chapter 45). Occasionally, long-term, lower-dose prophylactic antibiotic treatment may be necessary to prevent recurrent UTIs. Routine urinalyses should be performed every 2 to 4 months in asymptomatic animals, and follow-up urine cultures performed in animals with clinical signs of lower urinary tract inflammation.

Calcium oxalate uroliths. A medical treatment for the dissolution of oxalate urolithiasis has not yet been developed. A moderate restriction of protein, calcium, oxalate, and sodium intake, with a normal intake of phosphorus, magnesium, and vitamins C and D, is recommended to prevent recurrence of calcium oxalate uroliths after surgical removal (e.g., Hill's Canine Prescription Diet u/d is recommended for this). Increased dietary sodium intake may result in an increase in the urinary excretion of calcium and therefore should be avoided. Potassium citrate, given orally, may help prevent recurrence of calcium oxalate uroliths because citrate complexes with calcium, thereby forming a relatively soluble calcium citrate. In addition, it results in mild urine alkalinization, which increases the solubility of calcium oxalate. However, because overzealous urine alkalinization may result in the formation of calcium phosphate uroliths, this should be avoided. The recommended dose of potassium citrate is 40 to 75 mg/kg, administered orally q12h.

Thiazide diuretics have also been recommended to decrease the urinary excretion of calcium; hydrochlorothiazide (2 mg/kg, administered orally q12h) has been shown to reduce urine calcium excretion in dogs. This effect was enhanced by combining the treatment with the u/d diet.

Urate uroliths. The medical dissolution of urate uroliths that are not associated with hepatic insufficiency (e.g., PSSs) should include a diet low in protein and nucleic acids, alkalinization of the urine, xanthine oxidase inhibition, and the elimination of UTIs. Hill's Canine Prescription Diet u/d has a reduced protein and purine content and produces alkaline urine; therefore it is recommended for the dissolution and prevention of urate uroliths. The u/d diet decreases the hepatic formation of urea and hence renal medullary hypertonicity and urine-concentrating ability. In addition, allopurinol, a competitive inhibitor of the enzyme xanthine oxidase, which converts hypoxanthine to xanthine and xanthine to uric acid (Fig. 46-8), should be administered orally at a dose of 10 to 15 mg/kg q12h or once daily, and, if necessary, sodium bicarbonate or potassium citrate should be administered orally to maintain a urine pH of 7.0. The dose of the urine alkalinizer has to be individualized for each animal. Potassium citrate is available in a wax matrix tablet (Urocit-K; Mission Pharmacal, San Antonio, Texas). Treatment can be started with a one-quarter tablet q8h and the dosage adjusted up or down based on the urine pH. Higher doses of allopurinol especially if combined with higher protein diets, increase the risk of xanthine urolith formation. It is

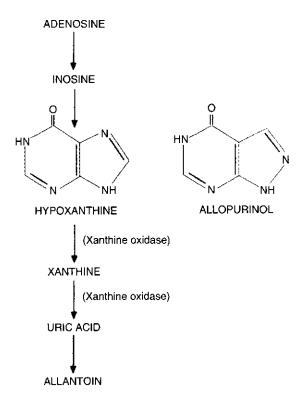


FIG 46-8
Metabolism of purine adenosine and a comparison of the structures of hypoxanthine and allopurinol.

unknown if the long-term use of allopurinol to prevent the recurrence of urate uroliths increases the risk of xanthine uroliths. The benefits of allopurinol may, however, outweigh the risks in animals that have had multiple episodes of urate urolithiasis. Just as in the management of struvite uroliths, any UTI should be appropriately treated because urease-producing organisms will increase the urine ammonium ion concentration and potentiate ammonium urate crystal production.

In dogs with urate urolithiasis secondary to severe hepatic insufficiency, the underlying disorder should be corrected if possible. If hepatic function can be improved (e.g., surgical correction of a PSS) and the urine becomes undersaturated with ammonium and urate ions, uroliths may dissolve spontaneously. Even though spontaneous dissolution after surgical correction of a PSS is possible, it is usually recommended that a cystotomy be performed to remove uroliths at the time of PSS correction. In dogs with inoperable PSS or microvascular dysplasia, the k/d or l/d diet may be used to help decrease urine saturation with ammonium urate and reduce signs of hepatoencephalopathy.

**Silicate uroliths.** Although the medical dissolution of silicate uroliths is not yet feasible, recommended ways to decrease recurrence after surgical removal include a dietary change, increasing the urine volume, and urine alkalinization. Hill's Canine Prescription Diet u/d may be beneficial because it contains low amounts of silicates and produces alkaline urine. In addition, in certain regions soil may contain high concentrations of silicate; therefore the consumption of dirt and grass should be discouraged.

Cystine uroliths. Recommendations for the medical dissolution and prevention of cystine uroliths include a reduction in the dietary intake of protein and methionine, alkalinization of the urine, and the administration of thiolcontaining drugs. Hill's Canine Prescription Diet u/d is appropriate because it has a very low protein content, produces alkaline urine, and decreases the urine-concentrating ability. Urine pH should be maintained at approximately 7.5, with potassium citrate given orally if necessary. Treatment can be started with a one-quarter tablet q8h and the dosage adjusted up or down depending on the urine pH (see urate section above). Sodium bicarbonate or sodium chloride supplementation should be avoided because the resulting natriuresis may enhance cystinuria. d-Penicillamine forms a disulfide compound with cysteine and therefore decreases the cystine content of the urine (Fig. 46-9). This disulfide compound is approximately 50 times more soluble than cystine in urine. d-Penicillamine may interfere with surgical wound healing, and treatment should not be initiated earlier than 2 weeks after surgery. Other possible infrequent or rare adverse effects of d-penicillamine include immune complex glomerulonephritis, fever, and skin hypersensitivity. Another thiol-containing drug, N-(2-mercaptopropionyl)-glycine (MPG), increases the solubility of cystine in urine by means of a disulfide exchange reaction similar to that produced by d-penicillamine and may have fewer adverse effects. The dose of MPG recommended for dogs for urate urolith dis-

FIG 46-9
Structures of cystine, cysteine, d-penicillamine, and cysteine-penicillamine disulfide.

solution is 15 to 20 mg/kg, administered orally q12h. Thiol-containing drugs should be used along with Hill's Canine Prescription Diet u/d if necessary to prevent cystine urolith formation.

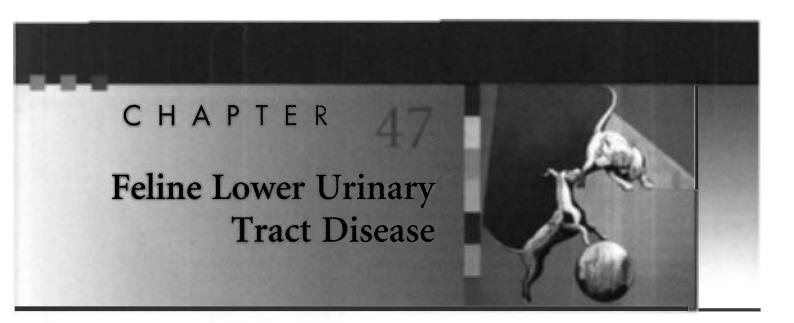
## MONITORING THE PATIENT WITH UROLITHIASIS

Whenever medical dissolution of uroliths is being attempted, the patient should be reexamined at least monthly. A complete urinalysis should be performed, and abdominal radiographs or ultrasonography should be done to assess urolith size. If urinalysis findings are suggestive of a UTI, bacterial culture and sensitivity testing should be performed and antibiotic treatment initiated or adjusted accordingly. If the urolith has not decreased in size after 2 months of dissolution treatment, the clinician should reassess owner compliance, the control of infection, and urolith type and consider removing the urolith surgically.

Uroliths recur in up to 25% of dogs, and it is not uncommon for individual dogs to have three or more episodes of urolithiasis in their lifetimes. The likelihood of recurrence appears to be greatest in dogs with metabolic uroliths (calcium oxalate, urate, and cystine uroliths) or a familial predisposition (e.g., Miniature Schnauzers with struvite uroliths). Therefore appropriate preventive measures and frequent reevaluations are important in such dogs.

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### CHAPTER OUTLINE

Etiology and Pathogenesis Clinical Features and Diagnosis Management

Feline lower urinary tract disease (FLUTD) is characterized by one or more of the following clinical signs: pollakiuria, hematuria, dysuria-stranguria, inappropriate urination, and partial or complete urethral obstruction. These clinical signs have historically been termed *feline urologic syndrome*; however, this syndrome is not a single disease entity. The definition of the syndrome has varied among studies and authors, and it is difficult to interpret the literature without a broader definition that includes all disorders associated with FLUTD.

FLUTD has been reported to occur in 0.34% to 0.64% of all cats, and it is thought to be the reason for 4% to 10% of all feline admissions to veterinary hospitals. It appears to be equally prevalent in male and female cats, although overweight cats are thought to be at higher risk for FLUTD. Indoor cats are also reported to be more predisposed to FLUTD than outdoor cats; however, because the urination habits of indoor cats are more closely observed than those of outdoor cats, this may be an observational difference. Most feline lower urinary tract disorders occur in cats between 2 and 6 years of age, with a higher prevalence in the winter and spring months. Between 30% and 70% of cats that have one episode of FLUTD will have a recurrence.

The reported mortality rates for cats with FLUTD range from 6% to 36%. Hyperkalemia and uremia are major causes of death in male cats with urethral obstruction; however, some cats with recurrent FLUTD are euthanized because their owners are unwilling to incur the expense of repeated treatment, diagnostics, or hospitalization necessary to relieve urethral obstruction. Chronic kidney disease (CKD) secondary to ascending pyelonephritis is a possible long-term sequela or complication of FLUTD, especially if there have been repeated urethral catheterizations.

### **Etiology and Pathogenesis**

FLUTD can be divided into two broad categories according to the presence or absence of an identifiable cause of the urinary tract disease. Uroliths, urinary tract infection (UTI), anatomic abnormalities (e.g., urachal remanants, urethral strictures), trauma, irritant cystitis, neurologic disorders, behavioral abnormalities, and neoplasia can all cause or mimic FLUTD. In many cases, despite a thorough diagnostic evaluation, the cause of FLUTD remains unknown and is classified as idiopathic.

**Uroliths.** FLUTD may occur in association with uroliths, microcalculi, and/or crystal-containing mucous urethral plugs. Struvite and calcium oxalate are the most common feline uroliths. As with canine urolithiasis, there must be a sufficiently high concentration of urolith-forming constituents in the urine, a favorable pH, and adequate time in the urinary tract for crystals/uroliths to form.

Approximately 45% of the uroliths in cats consist either entirely or predominantly of struvite. Most struvite uroliths form in the urinary bladder of young cats, and in contrast to dogs, most feline struvite uroliths form in sterile urine. When a bacterial infection is present, the most common organism is a urease-producing *Staphylococcus* sp. Tamm-Horsfall mucoprotein, secreted by the renal tubules, is the major protein found in feline struvite uroliths. It may also play a role in the pathogenesis of urethral plugs that may contain struvite crystals.

Urethral obstruction is more common in the male cat; the length and diameter of the urethra play a relevant role in this. Many obstructions are caused by mucus- and/or struvite-containing plugs that lodge in the penile urethra. Uroliths may lodge in any portion of the urethra, including sections proximal to fibrous connective tissue strictures resulting from previous injuries. Local inflammation that develops in response to urethral calculi or plugs may exacerbate the obstruction by causing urethral edema. Iatrogenic trauma created by urethral catheterization may also cause urethritis or inflammation of the periurethral tissue, leading to urethral compression.

In addition to struvite uroliths, other types of uroliths, including calcium oxalate and urate stones, can cause signs

of FLUTD. Calcium oxalate uroliths account for approximately 45% of feline uroliths, and urate uroliths constitute approximately 5%. According to one study, Burmese, Persian, and Himalayan cats may be at higher risk for calcium oxalate urolithiasis. Calcium oxalate uroliths are also more common in neutered male cats than in female cats, their prevalence is higher in older animals, and they occur more frequently in the kidneys than struvite uroliths do. Calcium oxalate uroliths are becoming more prevalent in cats, and this may be related to the widespread use of acidifying diets designed to prevent struvite-related FLUTD. Epidemiologic studies indicate that cats fed diets low in sodium or potassium or formulated to maximize urine acidity have an increased risk of developing calcium oxalate uroliths but a decreased risk of developing struvite uroliths. Another retrospective study suggested that feeding cats urine-acidifying diets, feeding cats a single brand of cat food, and maintaining cats in an indoor-only environment were factors associated with the development of calcium oxalate urolithiasis. The increase in prevalence of calcium oxalate uroliths in cats may also correlate with the observation that cats are living longer lives than they were 10 to 15 years ago. Finally, because the prevalence of calcium oxalate uroliths is also increasing in people and dogs, there may be unidentified environmental factors common to all three species influencing the development of these uroliths.

**Urinary tract infection.** A primary bacterial infection of the feline urinary tract, although rare in young cats compared with dogs, may also cause the clinical signs observed in FLUTD. Usually, UTI will occur secondary to altered normal host defense mechanisms that allow bacteria to colonize the bladder or urethra. Complete voiding (bladder content washout) is a major host defense mechanism against bacterial infection. Therefore anatomic abnormalities, partial obstructions, or detrusor atony that may interfere with normal voiding can result in an increased urine residual volume. Chronic inflammation of the urinary bladder with fibrosis and thickening of the bladder wall may also cause decreased detrusor tone and incomplete voiding. Perhaps the most important factor predisposing to the development of a secondary bacterial cystitis in association with FLUTD is urethral catheterization (especially placement of indwelling urinary catheters) combined with fluid therapy and the formation of dilute urine that has decreased antibacterial properties.

From time to time, researchers have implicated viruses, including feline calicivirus, bovine herpesvirus 4, and feline syncytia-forming virus, in the pathogenesis of FLUTD. The finding of bovine herpesvirus 4 antibodies in cats and the detection of calicivirus-like particles in the crystalline-mucous urethral plugs of male cats have sparked renewed interest in the possibility of a viral component in the syndrome (Osborne et al., 1999). Whether viruses play a major role remains to be determined.

Miscellaneous causes of feline lower urinary tract disease. In previous studies of cats with naturally occurring FLUTD, approximately 25% had vesicourachal diverticuli (Fig. 47-1). These may be congenital or acquired;

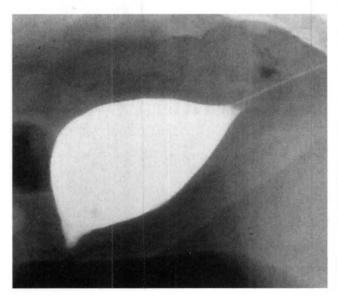


FIG 47-1
Positive-contrast—enhanced cystogram of a feline bladder showing a urachal remnant.

the acquired diverticuli are observed primarily in cats older than 1 year, with a mean age of 3.7 years. Male cats are twice as likely to acquire the abnormality as female cats, and increased intravesical pressure and bladder inflammation during urethral obstruction may play a major role in its pathogenesis. Although a urachal diverticulum may be an incidental finding in an asymptomatic cat, hematuria and dysuria are frequently noted clinical signs. Vesicourachal diverticuli are currently thought to develop secondary to FLUTD and increased intravesical pressure and are not thought to be a major initiating factor.

Idiopathic feline lower urinary tract disease. In large retrospective studies of cats with FLUTD conducted at the University of Minnesota and Ohio State University, a cause could not be found in 54% and 79% of the cats, respectively. Researchers at Ohio State University have found numerous similarities between cats with idiopathic FLUTD and women with interstitial cystitis. These similarities include chronic irritative voiding patterns, sterile urine, a prominent bladder mucosal vascularity with spontaneous hemorrhages observed during cystoscopy, decreased mucosal production of glycosaminoglycan, and increased numbers of mast cells and sensory afferent neurons in bladder mucosal biopsy samples. The cause of interstitial cystitis in women is also unknown. A decreased urine volume and decreased frequency of urination may facilitate the development of FLUTD. Possible causes of a decreased urine volume and frequency of urination include a dirty or poorly available litter box; decreased physical activity as a result of cold weather, castration, obesity, illness, or confinement; and decreased water consumption because of water taste, availability, or temperature. Stress may also contribute to the development of the clinical signs of urinary tract disease. Increased plasma concentrations of noradrenaline have been

documented in cats with idiopathic FLUTD. Increased noradrenaline could increase uroepithelial permeability, increase nociceptive nerve fiber (C-fiber) activity, and activate neurogenic bladder inflammatory responses. Furthermore, decreased cortisol concentrations have been observed when corticotropin-releasing factor and adrenocorticotropic hormone concentrations are increased in cats with idiopathic FLUTD, indicating the possibility of reduced adrenocortical reserve. Although the role of stress is difficult to prove, it is often implicated; the history provided by owners frequently points to a recent association with boarding, cat shows, a new pet or baby in the home, a vacation, or cold or rainy weather. Additional stressors in multiple cat households may include intercat aggression brought on by competition for access to water, food, litter boxes, and space.

### **Clinical Features and Diagnosis**

The clinical signs of FLUTD depend on the component of the disease complex present (Box 47-1). Unobstructed cats usually have pollakiuria, dysuria-stranguria, and microscopic or gross hematuria, and they urinate in inappropriate places, often in a bathtub or sink (see also Chapter 41). These clinical signs may be readily apparent in cats that live indoors but may be missed in cats that live primarily outdoors.

In male cats with urinary obstruction, the presenting signs depend on the duration of the obstruction. Within 6



BOX 47-1

Clinical Signs Associated with Lower Urinary Tract Inflammation in Cats

### **Cystitis-Urethritis**

Hematuria

Pollakiuria

Dysuria-stranguria

Vocalizing during voiding

Licking at genitalia

Urination in inappropriate places

### **Partial or Complete Urethral Obstruction**

Inability to urinate, straining in the litter box Hiding behavior

Vocalizing during voiding attempts

Painful abdomen

Licking at genitalia

Congested penis extended from prepuce Signs of postrenal azotemia/uremia

Depression

Weakness

Anorexia

Emesis

Dehydration

Hypothermia

Acidosis and hyperventilation

Electrolyte disturbances (hyperkalemia)

Bradycardia

to 24 hours, most obstructed cats will make frequent attempts to urinate, pace, vocalize, hide under beds or behind couches, lick their genitalia, and display anxiety. If the obstruction is not relieved within 36 to 48 hours, clinical signs characteristic of postrenal azotemia, including anorexia, vomiting, dehydration, depression, weakness, collapse, stupor, hypothermia, acidosis with hyperventilation, bradycardia, and sudden death, may occur.

On physical examination an unobstructed cat will be apparently healthy, except for a small, easily expressed bladder. The bladder wall may also be thickened. Abdominal palpation may be painful for the unobstructed cat; however, the obstructed cat always resents manipulation of the caudal area of the abdomen. The most relevant finding during physical examination of an obstructed cat is a turgid, distended bladder that is difficult or impossible to express. Care should be exercised when manipulating the distended bladder, however, because the wall has been injured by the increased intravesical pressure and is susceptible to rupture. In the cat with urethral obstruction, the penis may be congested and protrude from the prepuce. Occasionally, a urethral plug is observed to extend from the urethral orifice; in some cases the cat may lick its penis until it becomes excoriated and bleeds.

The diagnosis of urethral obstruction is usually straightforward and is based on historical and physical examination findings. In unobstructed cats with FLUTD, urinalysis usually reveals hematuria; if not, behavioral causes of abnormal urination should be considered (Box 47-2 and Fig. 47-2). Struvite-associated disease is likely in cats in which the initial urine pH is alkaline and struvite crystals are observed in the urine sediment. Radiography or ultrasonography and urine cultures should be employed to rule out or identify overt urolithiasis and a urinary tract infection in cats with suspected struvite-associated disease, especially if there is no response to a magnesium-restricted, acidifying diet (see Fig. 47-2 and the section on management). In cats with FLUTD that have acidic urine, radiography or ultrasonography can help identify or rule out anatomic abnormalities (e.g., thickened bladder wall, polyps, tumors, nonstruvite-associated urolithiasis). Cystoscopy is also a valuable tool in cats with FLUTD. Nonspecific cystoscopic findings include prominent mucosal vascularity and submucosal petechial hemorrhages. Radiography (plain and double-contrast-enhanced cystography), ultrasonography, or cystoscopy and urine culture should be performed in all cats with recurrent FLUTD.

### Management

**Unobstructed cats.** The nature of the treatment for FLUTD depends on the clinical signs at presentation (see Box 47-2 and Fig. 47-2). Unobstructed cats with dysuriastranguria and hematuria will often become asymptomatic within 5 to 7 days of presentation whether therapy is instituted or not. Many cats are treated with antibiotics, and if clinical signs abate, a cause-and-effect relationship is often established in the minds of the clinician and cat owner. The clinician should remember, however, that more than 95%



BOX 47-2

### Diagnostic and Therapeutic Plan for Cats with Lower Urinary Tract Inflammation

- Rule out urethral obstruction; relieve obstruction, if present with no. 2 below.
- Assess degree of hyperkalemia with an electrocardiogram; measure serum urea nitrogen, creatinine, and potassium concentrations; and initiate IV fluid therapy if cat is obstructed and depressed.
- In both obstructed and unobstructed cats, obtain a urine sample by cystocentesis, if possible, for the evaluation of urine pH and urine sediment. Culture urine if there is evidence of a urinary tract infection (pyuria, bacteriuria).
- Manage cats with suspected struvite-associated FLUTD using a diet containing less than 20 mEq of magnesium per 100 kCal, and acidify urine (between 6.2 and 6.4) with ammonium chloride or methionine, if necessary.
- Obtain a urine sample in cats with non-struviteassociated FLUTD or in cats with struvite-associated FLUTD with persistent or recurring clinical signs:
  - a. If there is no evidence of urinary tract infection, examine the bladder using radiography or ultrasonography or examine the bladder and urethra using contrast-enhanced radiography or cystoscopy.
  - b. If there is evidence of urinary tract infection, perform bacterial culture and sensitivity testing and treat with an appropriate antibiotic. If signs persist or recur, examine the bladder using radiography or ultrasonography or examine the bladder and urethra with contrast-enhanced radiography or cystoscopy.
- 6. In cases of idiopathic FLUTD, try antiinflammatory treatment.

IV, Intravenous; FLUTD, feline lower urinary tract disease.

Clinical signs (dysuria/stranguria, hematuria, pollakiuria, inappropriate urination) Urinalysis Normal Abnormal (rule out behavioral (most likely abnormality and neurologic causes) is hematuria) Alkaline pH Acidic pH Struvite crystalluria No crystalluria Dietary trial (If bacteria (low Mg and urine or pyruria present) acidification) Quantative urine culture No growth Significant growth Antibiotic trial Response No response/ No response/ Response recurrence recurrence Survey and contrast radiographs or ultrasonography of urinary tract or cysto-urethroscopy Specific findings (e.g., Nonspecific findings (e.g., generalized bladder focal bladder wall thickening, tumor, polyps, uroliths) wall thickening, prominent mucosal vascularity, spontaneous submucosal petechial hemorrhages) Try anti-inflammatory treatment Surgery/biopsy if urine is bacteriologically sterile

FIG 47-2
Diagnostic and therapeutic flow chart for unobstructed cats with lower urinary tract disease.

of young cats with FLUTD have sterile urine and that the same results could be obtained by treating with numerous placebos.

If the initial urinalysis reveals an alkaline urine with struvite crystalluria, imaging of the urinary tract to rule out struvite uroliths is indicated. Urine culture and sensitivity tests should be performed if pyuria or bacteriuria is observed in the urine sediment, and appropriate antibiotics should be administered if urine cultures are positive. Cystocentesis is the ideal way to obtain urine for bacterial culture; if urine is obtained by any other method, a quantitative urine culture should be performed. Several sources of fresh water should be made available to the cat. The litter boxes should also be cleaned frequently and placed in convenient locations.

Hill's Feline Prescription Diet s/d can be used to effectively dissolve struvite uroliths. It takes an average of 36 days for sterile struvite uroliths to dissolve, whereas struvite uroliths associated with urease-producing bacterial infections in cats take an average of 79 days to dissolve. Antibiotic treatment in cats with struvite urolithiasis and a concurrent bacterial urinary tract infection should be determined on the basis of urine culture and sensitivity results and continued throughout the period of dissolution. The diet should be fed for 30 days beyond the point when the uroliths are no longer visible in radiographs.

If struvite crystalluria and alkaline urine recur repeatedly in cats with previous struvite uroliths, longer-term dietary therapy is warranted. Examples of diets that can be used to treat struvite-associated FLUTD as well as prevent recurrence include Hill's Feline Prescription Diet c/d (canned or dry), Science Diet Feline Maintenance (canned or dry), Iams pH/S, Purina UR-Formula Feline Diet, and Waltham Veterinarium Feline Control pHormula Diet. The composition of many over-the-counter cat foods is not constant; therefore it is difficult to make recommendations regarding their use. Ideally, the urine pH, measured 4 to 8 hours after feeding, should be maintained between 6.2 and 6.4. The aforementioned prescription diets are metabolized to form acid ions, which are excreted in the urine; it is rare, therefore, for these prescription diets not to maintain an acidic urine in cats. A urease-producing bacterial infection and dietary indiscretion should be identified or ruled out if alkaline urine is found to persist during dietary therapy.

In most cases of FLUTD, the urine is acidic and no struvite crystals are observed; therefore magnesium-restricted, acidifying diets are not recommended. In cats with persistent or recurrent clinical signs, a urine sample should be obtained by cystocentesis for urine culture, and plain abdominal radiography or ultrasonography, contrast-enhanced radiographic studies of the bladder and urethra, or cystoscopy should be performed to identify or rule out anatomic abnormalities if the urine is bacteriologically sterile (see Box 47-2 and Fig. 47-2). Numerous agents, including antibiotics, tranquilizers, anticholinergics, analgesics, antispasmodics, glycosaminoglycans, amitriptyline, and antiinflammatory drugs (e.g., dimethylsulfoxide, glucocorticoids, and nonsteroidal antiinflammmatory drugs [NSAIDs]), have been recom-

mended for the treatment of FLUTD in cats; however, no controlled studies have demonstrated the efficacy of any of these agents. Oxybutynin and propantheline are antispasmodic drugs that may alleviate pollakiuria in some cats, and buprenophine (0.005 to 0.01 mg/kg administered intravenously or intramuscularly q4-8h) or butorphanol (0.2 to 0.8 mg/kg administered intravenously or subcutaneously q2-6h or 1.5 mg/kg administered orally q4-8h) can be used as an analgesic. It must be kept in mind that in controlled studies, more than 70% of cats with idiopathic FLUTD have appeared to respond to placebo treatments (e.g., lactose, wheat flour).

In cats that will accept the change, switching from a dry diet to a canned diet to help increase water intake and decrease urine concentration is often associated with improvement. Decreasing stress and improving quality of life may also be very important factors in the management of cats with idiopathic FLUTD. Increasing the number of litter boxes and keeping them clean may help decrease stress in multiple cat households. Similarly, providing access to several sources of fresh food and water may help. Cats may also benefit from increased play activities and increased access to private space. Finally, pheromone therapy (Feliway CEVA Animal Health, Libourne, France) may produce a calming effect and help reduce stress.

**Obstructed cats.** In cats with a urethral obstruction, the relative urgency for relieving the obstruction depends on the physical status of the cat. Cats that are alert and not azotemic may be sedated for urethral catheterization without further diagnostic tests or treatment; however, in a depressed cat with urethral obstruction, the serum potassium concentration should be measured in-house or an electrocardiograph rhythm strip should be evaluated to assess the degree of hyperkalemia (see Box 46-1) and an intravenous (IV) catheter should be placed for the administration of normal (0.9%) saline solution before establishing urethral patency. If the electrocardiogram or blood tests confirm the presence of hyperkalemia, the cat should be treated aggressively to decrease serum potassium concentrations or counteract the effects of hyperkalemia on cardiac conduction (see Box 46-1).

The degree of restraint required for urethral catheterization depends on the cat's temperament and physical status. Physical restraint in a towel or cat bag, with or without the topical application of lidocaine, may be all that is required in a severely depressed cat. In cats requiring more restraint, ketamine HCl (1 to 2 mg/kg administered intravenously), an ultra–short-acting barbiturate (IV thiamylal sodium or thiopental sodium, 1 mg/kg titrated to effect), or propofol 6.6 mg/kg administered IV slowly over 60 seconds) may be used to effect. Because ketamine is eliminated by the kidneys, low IV doses (10 to 20 mg total) are frequently adequate for restraint. The administration of additional doses of ketamine should be avoided in severely azotemic cats.

A urethral obstruction may be relieved in some cases by penile massage and gentle expression of the bladder. If this does not result in urine flow, palpation of the urethra per rectum may dislodge a urethral plug or calculus. Sterile isotonic saline solution, administered through well-lubricated catheters or cannulas, should be used to hydropulse urethral plugs into the bladder. A variety of cannulas and catheters may be used for this purpose; however, nonmetal catheters with smooth, open ends are preferred to prevent iatrogenic damage to the urethral mucosa. Use of a strict aseptic technique is essential to prevent bacterial UTIs. If catheterizing the bladder proves difficult, cystocentesis with a 22-gauge or small needle may be performed to decrease the intravesical pressure and allow for the urethral obstruction to be backflushed into the bladder.

Indications for the placement of indwelling urinary catheters in male cats with obstructions that have just been relieved include the following: (1) an inability to restore a normal urine stream, (2) an abundance of debris that cannot be extracted via repeated bladder lavage, (3) evidence of detrusor atony in cats that cannot be manually expressed four to six times per day, or (4) intensive care of critically ill animals in which urine formation is being monitored as a guide to fluid therapy requirements. When an indwelling urinary catheter is necessary, again, strict aseptic technique should be used during placement. A soft red rubber feeding tube (3F to 5F) should be used; placing the feeding tube in the freezer for 30 minutes before use facilitates its passage. The catheter should be inserted only as far as the neck of the bladder; catheter passage should be stopped as soon as urine can be aspirated from the catheter. A closed urine-collection system should be used, and the catheter should be sutured to the prepuce and left in place for as short a time as possible (2 to 3 days is the average). An Elizabethan collar or tape hobbles are needed to prevent the cat from chewing out the sutures and removing the catheter. Phenoxybenzamine or prazosin treatment is often initiated at this time to decrease urethral spasms that can be stimulated by the indwelling catheter. Prophylactic antibiotic treatment is not recommended; however, the urine sediment should be examined daily for bacteria and white blood cells, and the urine cultured if necessary. Secondary bacterial UTIs are common in cats with indwelling urinary catheters receiving IV fluids to promote diuresis.

The degree of postrenal azotemia should be assessed by measuring the serum urea nitrogen, creatinine, and potassium concentrations. IV fluid therapy is indicated, especially in cats with azotemia. Maintenance therapy (approximately 60 to 70 ml/kg/day) and replacement therapy (percentage of dehydration  $\times$  body weight [in kilograms] = liters to administer) should be administered intravenously over 24 hours. The subcutaneous administration of a balanced electrolyte solution is an acceptable mode of fluid therapy in some cats once the initial uremic crisis is under control. Measurement of the urine volume every 4 to 8 hours will facilitate the administration of correct replacement therapy. A largevolume, postobstructive diuresis may develop in some cats, and IV fluid replacement therapy is essential in these animals. Serum urea nitrogen, creatinine, and serum electrolyte concentrations should be reassessed as needed, depending on

the degree of azotemia and the response to treatment, to ensure the adequate recovery of renal function. Occasionally, hypokalemia occurs in a cat with a prolonged and severe diuresis. In addition, if severe hematuria persists, the hematocrit should be monitored once or twice daily.

Detrusor atony is fairly common in cats obstructed for more than 24 hours and is associated with bladder over-distention. If the bladder can be expressed four to six times per day, an indwelling catheter may not be necessary. If the bladder cannot be expressed at least four times per day, an indwelling catheter is indicated. Bethanechol (2.5 mg q8h administered orally) may be administered to stimulate detrusor contractility only after the finding of a wide urine stream or the placement of an indwelling urinary catheter has confirmed that the urethra is patent. Acepromazine and phenoxybenzamine can significantly lower intraurethral pressures in anesthetized, healthy, intact male cats, and therefore these drugs may also be helpful in the management of a functional urethral obstruction in cats with FLUTD.

Perineal urethrostomy is rarely required for the emergency relief of a urethral obstruction. If the obstruction cannot be relieved by medical means, the condition of uremic cats must be stabilized before surgery is performed. Repeated cystocentesis should be done to keep the bladder empty until hyperkalemia, acidosis, and uremia resolve. Elective perineal urethrostomies are occasionally advisable in male cats with recurrent obstructions to decrease the likelihood of death from postrenal azotemia. However, a perineal urethrostomy does not decrease the risk of recurrence of clinical signs of cystitis, and it has been documented that cats with cystitis that undergo perineal urethrostomics are more susceptible to bacterial UTIs.

Probably the most important aspect of long-term patient monitoring is ensuring that the owner recognizes both the significance and the clinical signs of urethral obstruction. Owners of male cats with urinary obstruction must be warned of the risks of reobstruction, especially during the first 24 to 48 hours after the relief of an obstruction or the removal of an indwelling urinary catheter. Allowing the owner to palpate the distended bladder during the initial examination is a good way to teach him or her how to differentiate pollakiuria, dysuria-stranguria, and an obstruction. Any straining in the litter box should be cause for alarm in a male cat with a history of urethral obstruction, and careful observation for continued voiding of urine is essential for the early detection of a recurrence.

Follow-up urinalysis and urine culture should be performed 5 to 7 days after catheterization in all cats that have been catheterized to relieve a urethral obstruction. Because normal host defenses are bypassed when a catheter is introduced into the bladder, UTIs are common after catheterization, especially if an indwelling urinary catheter has been used. A follow-up urinalysis and urine culture should also be performed in all cats receiving corticosteroids because these may decrease immune system function (and decrease inflammation-related changes in the urine sediment) and predispose cats to the development of bacterial UTIs. Ascend-

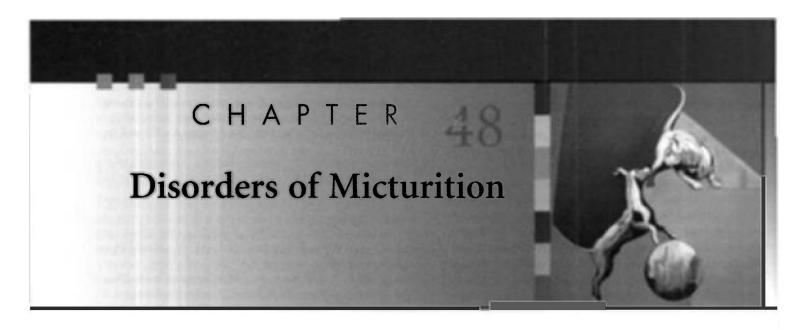
ing pyelonephritis is a significant concern in cats with any UTI, and it is a potential complication of FLUTD, especially if corticosteroids are used. Urethral obstruction caused by struvite uroliths or struvite-containing mucous plugs should be managed with dietary treatment designed to either dissolve the urolith or prevent recurrence, as previously described. Periodic urinalyses to measure pH are beneficial in cats with struvite-associated disease being managed by diet to prevent recurrent episodes. The urine pH 4 to 8 hours after eating should be 6.4 or less. Yearly urinalysis and bacterial culture are especially important in cats with perineal urethrostomies because the normal host defense mechanisms of the lower urethra have been surgically removed in these cats.

The prognosis for male cats with recurrent urethral obstruction is guarded, and perineal urethrostomy should be considered, especially if the second obstruction occurs during medical management designed to prevent recurrence. The prognosis for cats with recurrent nonobstructed FLUTD is fair to good, inasmuch as this syndrome is rarely life-threatening. Pyelonephritis, renal urolithiasis, and CKD are potential sequelae of recurrent nonobstructed FLUTD.

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### CHAPTER OUTLINE

PHYSIOLOGY OF MICTURITION

Etiology and Clinical Features of Disorders of Micturition DISTENDED BLADDER SMALL OR NORMAL-SIZE BLADDER

Diagnosis
INITIAL EVALUATION
PHARMACOLOGIC TESTING

Treatment
LOWER MOTOR NEURON DISORDERS
UPPER MOTOR NEURON DISORDERS
REFLEX DYSSYNERGIA
FUNCTIONAL URETHRAL OBSTRUCTION
URETHRAL SPHINCTER MECHANISM
INCOMPETENCE
DETRUSOR HYPERCONTRACTILITY
CONGENITAL DISORDERS
ANATOMIC URETHRAL OBSTRUCTION
Prognosis

Micturition is the normal process of the passive storage and active voiding of urine. Disorders of micturition encompass problems with urine storage (incontinence) and bladder emptying (urine retention). Urinary incontinence is the inappropriate passage of urine during the storage phase of micturition. The most common forms of urinary incontinence occur secondary to either increased detrusor contractility or decreased urethral outflow resistance. Conversely, decreased detrusor contractility or increased urethral outflow resistance can result in urine retention. Armed with an understanding of bladder and urethral neuroanatomy, as well as the mechanism of action of currently available drugs, clinicians are able to effectively control many disorders of micturition.

### PHYSIOLOGY OF MICTURITION

Micturition is controlled by a combination of autonomic and somatic innervation (Fig. 48-1). Parasympathetic inner-

vation to the bladder is provided by the sensory and motor portions of the pelvic nerve that arises from sacral spinal cord segments S1 to S3 (vertebral body L5). The sensory portion relays the sensation of bladder fullness as the stretch receptors associated with detrusor muscle fibers are activated. The motor portion of this parasympathetic innervation predominates during the voiding phase of micturition, with stimulation of the pelvic nerve resulting in the depolarization of pacemaker fibers throughout the detrusor muscle. The subsequent spread of excitation to adjoining muscle fibers through tight junctions of smooth muscle cells leads to contraction of the detrusor muscle.

The S1 to S3 spinal cord segments are also the source of the somatic innervation to the external urethral sphincter via the pudendal nerve. The motor portion of the pudendal nerve causes contraction of the skeletal muscle of the external urethral sphincter under voluntary control. The external urethral sphincter is located predominantly in the midportion of the female urethra and in the membranous portion of the male urethra. The pudendal nerve also has sensory and motor function to the perineal region, including the anal sphincter, vulva, and prepuce.

Sympathetic innervation to the bladder is provided by the hypogastric nerve and is composed of preganglionic fibers exiting spinal cord segments L1 to L4 in the dog (vertebral bodies L1 to L3) and L2 to L5 in the cat (vertebral bodies L2 to L4) and synapsing in the caudal mesenteric ganglion. Adrenergic fibers terminate in the detrusor muscle; stimulation of these fibers results in detrusor muscle relaxation, which facilitates urine storage. Adrenergic fibers innervate the smooth muscle fibers in the trigone and urethra; stimulation of these fibers causes contraction and formation of the functional internal urethral sphincter.  $\alpha$ -Adrenergic receptors also have a modulating effect on the external urethral sphincter.

The normal storage phase of micturition is governed by sympathetic autonomic domination, which causes the detrusor muscle to relax as a result of -adrenergic stimulation and the internal urethral sphincter to contract as a result of -adrenergic stimulation. Voiding is also consciously inhibited by the contraction of striated urethral muscles distal to

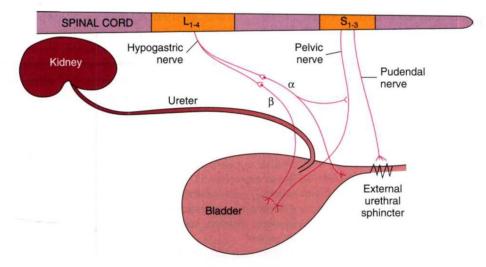


FIG 48-1
Autonomic and somatic innervation of the urinary bladder.

the bladder and involuntarily inhibited by a spinal reflex that tightens the external urethral sphincter when there is a sharp increase in intraabdominal pressure (e.g., during abdominal palpation or bladder expression, barking, coughing, sneezing, retching). Urinary incontinence occurs if the intravesical pressure exceeds the pressure exerted by the urethral sphincters.

Stretch receptors in the bladder send impulses through the pelvic nerve and spinal cord pathways to the thalamus and cerebral cortex when the urinary bladder fills and intramural tension exceeds the threshold. Voluntary control of voiding is mediated by the cerebral cortex through the pons (main micturition center), the cerebellum, and the reticulospinal tracts to the sacral nuclei. The voiding phase of micturition is characterized by parasympathetic activity. In this phase the detrusor muscle contracts secondary to cholinergic stimulation of the motor portion of the pelvic nerve. It is important to note that during this cholinergic-mediated detrusor contraction, the  $\alpha$  and  $\beta$ -adrenergic input to the internal and external urethral sphincters is reflexly inhibited at the level of the pons. When the bladder is empty, the normal sympathetic domination resumes and the detrusor muscle relaxes to allow filling to occur. The normal residual volume of urine after complete voiding is approximately 0.2 to 0.4 ml/kg (with a maximum of 10 ml) in both dogs and cats.

# Etiology and Clinical Features of Disorders of Micturition

Disorders of micturition can be divided into two major categories: those associated with a large or distended bladder and those associated with a small or normal-sized bladder (Table 48-1). Urine retention disorders associated with distended bladders include neurogenic disorders (upper [UMN] and lower [LMN] motor neuron disease, functional urethral obstruction, reflex dyssynergia) and anatomic obstructive disorders. Neurologic disorders may be caused by any condi-

tion that produces compression, damage, or degeneration of the spinal cord or pelvic nerve. Overdistention of the bladder for a prolonged time may also cause a neurogenic incontinence by decreasing bladder detrusor muscle tone (a type of LMN disorder). Dysautonomia in dogs and cats, an autonomic polyganglionopathy, also produces an LMN incontinence that is associated with weak and ineffective detrusor activity. On the other hand, urine leakage or incontinence disorders are usually associated with a small or normal-size bladder caused by increased detrusor contractility or decreased urethral outflow resistance. Congenital abnormalities of the urinary system (e.g., ectopic ureters, vaginal strictures) can also result in urinary incontinence associated with a small or normal-sized urinary bladder. It should be noted that urine leakage can occur with urine retention disorders when intravesical pressure exceeds outflow resistance. This type of urine leakage is referred to as paradoxic or overflow incontinence (discussed in greater detail later).

### DISTENDED BLADDER

Big, distended urinary bladders are usually easily palpated on physical examination, and the ease of bladder expression is an important part of patient assessment. If the distended bladder is easy to express, the underlying problem is usually decreased detrusor contractility. Conversely, if the bladder is difficult to express, increased outflow resistance should be suspected. Both functional (e.g., increased urethral tone caused by increased sympathetic tone or urethral spasm) and anatomic (e.g., urethral uroliths or trigonal masses) problems can cause increased outflow resistance. Urethral catheterization and/or positive contrast urethrography can be used to differentiate functional and anatomic causes of increased outflow resistance.

If neurologic lesions or deficits are detected during neurologic examination, the status of the bladder helps localize



**TABLE 48-1** 

Disorders of Micturition

### DISORDER **CAUSES** Distended Bladder Neurogenic Lesion to S1 to S3 spinal cord segment (at or below fifth lumbar Lower motor neuron disease vertebral body), neoplasia, trauma, cauda equina syndrome Trauma to pelvic nerve, detrusor atony, canine and feline dysautonomia Upper motor neuron disease Lesion cranial to \$1 spinal cord segment (above fifth lumbar vertebral body), intervertebral disk protrusion, neoplasia, trauma, fibrocartilaginous infarct, meningitis Cerebral disease, cerebellar disease, brainstem disease Reflex dyssynergia (detrusor-urethral dyssynergia) Unknown Functional urethral obstruction Urethral muscular spasm, often associated with urethral inflammation or trauma Anatomic outflow tract obstruction Urethral stricture, neoplasia, cystic or urethral calculi, granulomatous urethritis, prostatic disease Small or Normal-Sized Bladder Urethral sphincter mechanism incompetence Deficient bladder/urethral support, hormone-responsive Detrusor hyperreflexia or instability Bladder irritation, urethral irritation Congenital incontinence Ectopic ureters, patent urachus, urethral fistula (rectal or vaginal), pseudohermaphroditism, vaginal strictures

the lesion and classify the injury as either a UMN lesion (above the fifth lumbar vertebral body) or an LMN lesion (at or below the fifth lumbar vertebral body). The most characteristic sign of an LMN lesion affecting the bladder is a distended bladder that is easily expressed. An LMN injury affecting the bladder causes both sphincter and detrusor hyporeflexia; if the lesion involves spinal cord segments S1 to S3, both perineal and bulbospongiosus reflexes of the pudendal nerve are usually absent.

UMN lesions affecting the bladder result in a large, distended bladder that is difficult to express but easy to catheterize. Thoracolumbar spinal cord lesions causing paresis or paralysis are frequent causes of UMN bladder disorders. An animal with a UMN lesion has no voluntary control of micturition, and the urethral sphincter shows reflex hyperexcitability because the somatic efferents in the pudendal nerve are not inhibited, making expression difficult.

Reflex dyssynergia, or detrusor-urethral dyssynergia, is seen primarily in large-breed male dogs. The cause is usually difficult to determine but may include any of several neurologic lesions of the spinal cord or autonomic ganglia. Pathophysiologically, reflex dyssynergia results from the active contraction of the detrusor without relaxation of the internal or external urethral sphincters. Characteristic signs of reflex dyssynergia include normal or near-normal initiation of voiding, followed by a narrowed urine stream. Urine may be delivered in spurts, or flow may be completely disrupted and the dog will often strain to produce urine. After a while the dog will lower its leg and then often begins dribbling

urine while walking away. It is difficult to express urine from the bladder of a dog with reflex dyssynergia, but urethral catheterization is usually easily accomplished. With reflex dyssynergia, increased outflow resistance occurs when the dog tries to initiate voiding. A similar type of functional urethral obstruction has been described in three male dogs in which resting outflow resistance was increased (Lane, 2000). Prostatitis and a history of urethral calculi were associated with the functional urethral obstruction in two cases, respectively; the third case was diagnosed as idiopathic.

Anatomic outflow obstruction results in a big, distended bladder that is usually both difficult to express and catheterize. In some cases a catheter may be passed around an anatomic urethral lesion relatively easily, and a positive contrast retrograde urethrogram may be necessary to confirm the presence of a lesion.

Incontinence in an animal with a primary urine retention problem is called *paradoxic* or *overflow incontinence*. Urine leakage occurs in this case when intravesical pressure exceeds outflow resistance. Clinical signs associated with a functional or anatomic urethral obstruction include dribbling of urine, straining to urinate without producing urine, restlessness, and abdominal pain. The most common causes of anatomic urethral obstruction are calculi and neoplasia in dogs, and struvite/mucous plugs in cats; however, trigonal masses, urethral strictures, and granulomatous urethritis can also create obstructions to urine flow. Any type of prostatic disease in dogs may produce an outflow tract obstruction. Older male dogs with benign prostatic hyperplasia may be evaluated

because of stranguria and tenesmus; however, bacterial prostatitis, prostatic neoplasia, and prostatic abscesses are more likely causes of a urinary outflow tract obstruction. In patients with decreased detrusor contractility, paradoxic incontinence occurs earlier and at lower intravesicular pressures compared with patients that have either functional or anatomic outflow resistance problems.

### SMALL OR NORMAL-SIZE BLADDER

Causes of urinary incontinence associated with a small or normal-size bladder include increased detrusor contractility and decreased outflow resistance. Increased detrusor contractility is generally associated with bladder and or urethral irritation/inflammation that creates an urge to void that overcomes normal house-trained behavior. These patients often exhibit pollakiuria, dysuria, and stranguria and have inflammatory or hemorrhagic urine sediment findings. Conversely, in patients with decreased urethral outflow resistance, urine leakage is often most pronounced when the animal is asleep or relaxed. The voiding phase of micturition is usually normal in these patients, as is the urinalysis (unless complicated by an ascending urinary tract infection).

Detrusor muscle hypercontractility (also referred to as detrusor instability or urge incontinence) is the inability to control voiding owing to a strong urge to urinate. Inflammation of the bladder or urethra may trigger the voiding reflex by creating a sensation of bladder fullness. Clinical signs of this type of incontinence include pollakiuria, dysuria-stranguria, and frequently hematuria. A bacterial urinary tract infection is the most common cause in the dog, and sterile inflammation of the lower urinary tract is the most common cause in cats. Evidence of a urinary tract infection or inflammation revealed by urinalysis (e.g., bacteriuria, pyuria, or hematuria) initially supports the tentative diagnosis of urge or inflammatory incontinence. If clinical signs persist after appropriate treatment for the urinary tract inflammation has been initiated, further diagnostic studies, including ultrasonography, contrast-enhanced radiography, and cystoscopy, are indicated because infiltrative disease of the bladder (e.g., neoplasia, chronic cystitis), polyps, uroliths, or urachal remnants can result in pollakiuria and stranguria. It should also be noted that detrusor hyperreflexia/ instability may be a primary or idiopathic disorder that is not associated with bladder or urethral inflammation.

The preferred terminology for decreased urethral outflow resistance is urethral sphincter mechanism incompetence (USMI). This urethral sphincter dysfunction is most often observed in spayed, medium- to large-breed female dogs. Decreased tone in collagenous supporting structures of the urogenital tract caused by aging and/or decreased estrogen concentrations is thought to be the primary cause of USMI. Additional causes/complications may include abnormal bladder/urethral position (e.g., pelvic bladder), decreased responsiveness of  $\alpha$ -adrenergic urethral receptors, and obesity. Recently, abnormal caudad bladder movement with

the dog under anesthesia has been identified in bitches with USMI. This is thought to be due to deficient bladder and urethral support mechanism in these dogs. Estrogen and testosterone are believed to contribute to the integrity of urethral muscle tone by augmenting its responsiveness to  $\alpha$ -adrenergic innervation. Thus middle-age to older, spayed female dogs are prone to incontinence because of decreased estrogen concentrations. This incontinence is most pronounced when the animal is asleep or relaxed and often responds to estrogen replacement or α-adrenergic therapy. Less frequently, incontinence develops in male dogs after castration; the condition seems to occur most commonly in dogs castrated at an older age and often responds to α-adrenergic treatment or hormone replacement. Both processes are diagnosed on the basis of history, physical examination findings, urinalysis (lack of evidence of lower urinary tract inflammation), and the animal's response to therapy. Frequently,  $\alpha$ -adrenergic treatment (e.g., phenylpropanolamine) may be combined with hormone replacement treatment in severe cases of USMI.

Urinary incontinence in a young animal with a small or normal-size bladder may be associated with a variety of congenital defects of the urinary or genital systems. The most common defects are ectopic ureters and vaginal strictures, but patent urachus, urethrorectal and urethrovaginal fistulae, and female pseudohermaphroditism have also been associated with urinary incontinence. Ectopic ureters are most commonly observed in female dogs. Breeds in which the prevalence of ectopic ureters is high include Siberian Huskies, Miniature and Toy Poodles, Labrador Retrievers, Fox Terriers, West Highland White Terriers, Collies, and Cardigan and Pembroke Welsh Corgis. Ectopic ureters are rarely seen in cats, but the gender predisposition is reversed (i.e., the prevalence is higher in male than in female cats). USMI is a frequent concurrent problem in dogs with ectopic ureters or vaginal strictures.

The most common clinical sign associated with ectopic ureters is constant dribbling of urine, although dogs and cats with a unilateral ectopic ureter also may void normally. Because 70% of ectopic ureters in dogs terminate in the vagina, vaginoscopy may allow visualization of the opening of the ureter; however, the orifice may be difficult to see even if the vagina is fully distended with air. Intravenous urography and retrograde vaginourethrography are excellent diagnostic tests for characterizing the defect, although a recent study suggested that contrast computed tomography (CT) is the test of choice for the diagnosis of ectopic ureters. In contrast to the incontinence seen in animals with ectopic ureters, incontinence associated with a vaginal stricture is often intermittent, occurring with changes in body position. Vaginal strictures can be diagnosed by digital vaginal examination, vaginoscopy, or contrast-enhanced vaginography.

Incontinence may also be caused by cognitive disorders (CDs), decreased bladder capacity, or decreased mobility in senior animals. Polyuric-polydipsic disorders, such as chronic kidney disease (CKD) in senior animals, also often exacer-

bate incontinence. Likewise, use of diuretic and corticosteroid medications should be avoided, if possible, in incontinent animals because of their negative effects on urine-concentrating ability.

### Diagnosis

Clinical features of disorders of micturition often help the clinician discern the underlying problem. For example, if continuous urinary incontinence has been present from birth, the likely underlying problem is a congenital anomaly. Incontinence associated with hematuria, pollakiuria, and dysuria-stranguria usually indicates the presence of inflammation of the bladder, urethra, or both. Inappropriate dribbling of urine during sleep or relaxation indicates USMI, and leakage of urine in female dogs associated with postural changes may point to the pooling of urine behind a vaginal stricture. Dogs with pelvic bladders, which is a more caudal abdominal location in which the bladder neck is caudal to the pecten of the pubic bone (Fig. 48-2), can also have urethral sphincter incompetence that results in urinary incontinence. All these forms of incontinence are usually associated with a small or normal-size bladder.

Dysuria and stranguria that occur in association with an abnormal or absent urine stream are typical of an obstructive uropathy. Urethral obstructions may be caused by anatomic (e.g., uroliths, tumors) or functional (e.g., reflex dyssynergia) problems. Urinary incontinence that occurs in association with trauma or pelvic surgery is usually neurogenic in origin (LMN disease); if paresis or paralysis is present, the lesion is usually above the fifth lumbar vertebral body and is a UMN lesion. Obstructive uropathies

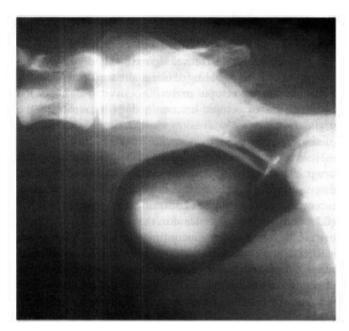


FIG 48-2
Double-contrast—enhanced cystogram showing a pelvic bladder in a 2-year-old spayed female Doberman Pinscher with urethral sphincter mechanism incompetence.

and UMN and LMN disorders result in large, distended bladders.

As noted earlier, incontinence in senior animals may be caused by CDs, a decreased bladder capacity, or decreased physical control. Physical problems in such animals, especially polyuric disorders and disabilities that impair mobility, should be identified and treated. Polyuria and polydipsia can trigger urge incontinence by placing continual stress on the bladder wall and urethral sphincter; however, in these cases the urine volume is large. A normally completely house-broken animal with polyuria and polydipsia may start urinating in the house if it does not have frequent access to the outdoors. If increased thirst and large urine volume are described by the owner, appropriate diagnostic tests should be performed to identify conditions that cause polydipsia and polyuria (e.g., diabetes mellitus, pyometra, CKD, hyperadrenocorticism, hypercalcemia).

Owners frequently mistake submissive urination, which may be a normal behavioral pattern of young dogs, with urinary incontinence. Other voiding patterns that are construed by some owners as incontinence are the urine marking used by male and occasionally female animals and inappropriate elimination behavior problems. The owner's description of the animal's voiding pattern may reveal a behavioral basis for the abnormal micturition, although a complete physical examination and a urinalysis should always be performed to identify or rule out a urinary tract disorder.

### INITIAL EVALUATION

The age of onset, reproductive status of the animal, age at neutering, current medications, and history of trauma or previous urinary tract disorders are important anamnestic points to cover during the history-taking in an animal with any disorder of micturition. The physical examination should include evaluation of the perineum for evidence of urine scalding or staining. A thorough palpation of the bladder to assess its size and wall thickness and a rectal examination to assess anal tone, the prostate gland, the pelvic urethra, and the trigone region of the bladder should be performed in all cases. A digital vaginal examination is also indicated, and vaginoscopy may be used to help identify congenital defects (e.g., vaginal strictures, ectopic ureters) in larger female dogs.

A neurologic examination should include evaluation of the perineal and bulbospongiosus reflexes. The perineal reflex causes the anal sphincter to contract and the tail to ventroflex in response to pinching the perineal skin. The bulbospongiosus reflex causes the anal sphincter to contract in response to gentle compression of the bulb of the penis or the vulva. Both these reflexes depend on an intact pudendal nerve (sensory and motor) and spinal cord segments S1 to S3. If both reflexes are normal, the pudendal reflex arc is intact. Because of their common origin, injury to the pudendal nerve may also affect the pelvic nerve.

Dogs should be walked outside so that the voiding posture and urine stream size and character can be observed. Imme-

diately after the animal has attempted to void, the bladder should be palpated to determine the residual volume (normal residual volume is approximately 0.2 to 0.4 ml/kg). Catheterization is indicated to quantify the residual volume if a large bladder is palpable after voiding (in male dogs, however, behavioral urine marking can make assessment of residual urine volume difficult).

Urinalysis should be performed in all animals with urinary incontinence. If a urine culture is indicated, cystocentesis is the preferred method of collection; however, animals with a distended bladder should be catheterized instead to empty the bladder and prevent the problem of urine leaking from the cystocentesis site. Additional diagnostic testing that can be accomplished at many referral centers includes cystoscopy and urethral pressure profilometry (UPP). Cystoscopy allows direct visualization of the urethral and bladder mucosa and the ability to obtain mucosal specimens for culture and histology. The functional length of the urethral sphincter and the urethral closure pressure can be determined via UPP, which is usually performed in conscious patients. A flexible catheter with a side port is passed through the urethra, and after the bladder has been emptied, the catheter is connected to a pressure transducer and a withdrawal arm (that pulls catheter back through the urethra at a constant rate). Saline is then infused through the catheter as it is withdrawn, and the resistance to flow (pressure) is recorded versus distance traveled. (See additional descriptions of bladder and urethral function testing in Chapter 42.)

### PHARMACOLOGIC TESTING

Frequently, the diagnosis of disorders of micturition is based to some degree on the animal's response to pharmacologic testing or therapy. For example, detrusor hypocontractility should improve in response to a parasympathomimetic drug (e.g., bethanechol), and decreased urethral tone should respond to  $\alpha$ -adrenergic agents (e.g., phenylpropanolamine) or hormone replacement therapy. Increased urethral tone is treated with  $\alpha$ -sympatholytics (e.g., phenoxybenzamine) and striated muscle relaxants (e.g., diazepam). Detrusor hypercontractility often responds to treatment of the underlying inflammatory process, such as bacterial cystitis or urolithiasis; however, smooth muscle antispasmodics (e.g., oxybutynin) and parasympatholytics (e.g., propantheline) may be useful in cases of severe inflammation.

### **Treatment**

### **LOWER MOTOR NEURON DISORDERS**

Animals with LMN diseases resulting from sacral spinal cord lesions or dysautonomia require expression or strict aseptic catheterization of their bladder at least three times per day. Urinalysis or examination of the urine sediment should be performed weekly, and a urine bacterial culture should be performed if there is any evidence of a urinary tract infection.

Care should be taken to prevent urine scalding by applying petroleum jelly to the perivulvar or peripreputial and abdominal skin. Bethanechol may be administered to increase detrusor contractility if the urethra is confirmed to be patent by bladder expression (5–15 mg/dog PO q8h; 1.25–5 mg/cat PO q8h). Adverse effects of bethanechol include salivation, vomiting, diarrhea, or coliclike signs that indicate intestinal cramping. These signs usually appear within 1 hour of drug administration; if they are observed, the dose of bethanechol should be decreased.

To manage detrusor atony, the bladder must be expressed or urinary catheterization done intermittently to keep the bladder empty for a period of days to weeks. A closed urine-collection system should always be used with indwelling catheters. Urinalysis should be performed every 3 or 4 days and a urine bacterial culture and antibiotic sensitivity testing done if there is any evidence of urinary tract inflammation. Bethanechol may be administered to increase detrusor contractility but only after increased outflow resistance has been ruled out.

### **UPPER MOTOR NEURON DISORDERS**

The nature of the management of animals with a UMN lesion affecting the bladder depends on whether the animal has an autonomic bladder. A reflex, or autonomic, bladder often develops 5 to 10 days after a spinal cord injury, and it occurs because stretching of the bladder wall stimulates a local reflex arc that results in detrusor contraction. There is no cortical perception or voluntary control, and initially voiding is usually incomplete, resulting in a large urine residual volume. Treatment in an animal before an autonomic bladder develops should include aseptic catheterization three times per day. The use of corticosteroids for the treatment of neurologic disease may cause polyuria, necessitating more frequent catheterization to prevent overdistention of the bladder. Corticosteroids also predispose animals to urinary tract infections. During the initial stages of treatment, urinalysis or urine sediment examination should be performed every 3 or 4 days, and urine bacterial culture and antibiotic sensitivity testing should be performed if there is evidence of urinary tract inflammation (corticosteroids frequently mask signs of inflammation). Because these animals are usually in pain and reluctant to move, it is important to prevent urine scalding. The use of elevated racks or absorbent bedding is indicated, and petroleum jelly applied around the perineum or prepuce may minimize urine scalding.

After an autonomic bladder develops, the bladder should be palpated after urination to determine the residual urine volume. It may still be necessary to catheterize the bladder two or three times per day to minimize urine stasis. Urinalyses should continue to be done on a monthly schedule (weekly if the animal is receiving corticosteroids), and owners should be instructed to bring in a urine sample if a change in urine color or odor is noted. Nursing care to prevent urine scalding should be continued.

### REFLEX DYSSYNERGIA

Reflex dyssynergia often responds to pharmacologic management; however, a therapeutic response may not be seen for several days. Drugs commonly used include an  $\alpha$ -blocker (e.g., prazosin or phenoxybenzamine), a somatic muscle relaxant (e.g., diazepam), and occasionally bethanechol. Intermittent urinary catheterization should be performed as necessary to keep the bladder small and combat detrusor atony that may be caused by overdistention of the bladder.

Phenoxybenzamine has a slow onset of action, and the dose should be increased only at 3- to 4-day intervals. The urine stream should be evaluated to gauge drug effectiveness. If the stream is weak but continuous and of normal diameter, bethanechol may be used to increase detrusor contractility; however, it must not be used until the functional urethral obstruction has been relieved. If the urine stream is intermittent or narrowed, increased doses of diazepam or phenoxybenzamine or both may be required. Because diazepam has a very short duration of action (approximately 1 to 2 hours when administered orally), administering it 30 minutes before walking the animal sometimes aids in the management of reflex dyssynergia. It may be several weeks before a correct combination of drugs is determined, however, and drug dosages may have to be modified over time. Periodic urinalyses are indicated to detect urinary tract inflammation or infection at an early stage.

Hypotension is the major adverse effect of phenoxybenzamine, and the dose should be decreased immediately if the animal shows any indication of lethargy, weakness, or disorientation. In most cases the dosage of phenoxybenzamine should be increased only if a favorable response is not observed after 3 or 4 days; rapid dose changes should be avoided. Nausea is an adverse effect that can be minimized by administering the medication with a small meal. Glaucoma is a rare complication of phenoxybenzamine treatment in people; it is unknown if this occurs in dogs.

### **FUNCTIONAL URETHRAL OBSTRUCTION**

Nonneurogenic functional urethral obstruction, in which resting as well as voiding urethral pressures are abnormally high, has been associated with prostatic disease; urinary tract infection; urethral muscular spasm; and urethral inflammation, hemorrhage, or edema in dogs and cats. Affected animals have clinical signs and histories similar to those in dogs with reflex dyssynergia. Resting urethral pressure profilometry is usually necessary to differentiate these two syndromes. When treatment of the underlying disorder fails to decrease the increased outflow resistance,  $\alpha$ -blockers (e.g., prazosin or phenoxybenzamine) and skeletal muscle relaxants (e.g., diazepam) can be used.

# URETHRAL SPHINCTER MECHANISM INCOMPETENCE

The treatment of urinary incontinence associated with decreased sphincter tone includes hormone replacement or α-adrenergic drugs (or both). The usual induction therapy for estrogen-responsive incontinence consists of diethylstilbestrol (DES; 0.1 to 1.0 mg total administered orally q24h for 3 to 5 days). The frequency of administration is then decreased to the lowest possible dose that will maintain continence. Some dogs can be successfully tapered to a very low maintenance schedule (e.g., 0.1 to 1.0 mg per dog every 7 to 10 days). Phenylpropanolamine (1.5 to 2.0 mg/kg administered orally q8h) may be used as an alternative drug or in addition to DES. Owners of dogs receiving phenylpropanolamine should be cautioned to observe their dog for hyperexcitability, panting, or anorexia and to decrease the dose if these signs develop. Although initially administered three times per day, in some animals the dosing frequency of timed-release or precision-release phenylpropanolamine can be decreased to a once- or twice-daily schedule. Careful observation by the owner for recurrence of signs usually reveals when the dose needs to be increased. Dogs with increasing resistance to DES pose the greatest worry because the development of estruslike signs and bone marrow toxicity are possible adverse effects of higher-dose DES therapy. Endocrine alopecia is another possible adverse effect. If DESresistant dogs are not concurrently receiving phenylpropanolamine, a trial of it should be instituted before the DES dose exceeds recommended levels. \( \alpha \)-Adrenergic drugs are contraindicated in patients with systemic hypertension, mitral regurgitation, and anxiety disorders.

Urethral sphincter incompetence in neutered male dogs is best treated with  $\alpha$ -adrenergic drugs. If testosterone is to be used, it should be parenterally administered because most testosterone administered orally undergoes rapid hepatic degradation. Depository forms injected intramuscularly may be effective for 4 to 6 weeks. Male dogs receiving testosterone should have regular rectal examinations to evaluate prostate size. Testosterone should not be used in dogs that were previously neutered because of a testosterone-responsive disease (e.g., benign prostatic hypertrophy, perianal adenomas) or behavioral disorders (e.g., aggression).

In those patients with USMI refractory to hormone replacement and/or  $\alpha$ -adrenergic therapy, alternative treatments include gonadotropin-releasing hormone (GnRH) analogues and urethral bulking and surgical procedures. Increased concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) have been documented in spayed dogs, and GnRH analogues will downregulate production/secretion of LH and FSH. Submucosal collagen injections at the level of the internal urethral sphincter via urethroscopy can also be used as an adjunct treatment to increase urethral sphincter tone. Finally, surgical procedures such as colposuspension, cystourethropexy, and formation

of seromuscular urethral slings may benefit patients with USMI that is nonresponive to medical management.

### DETRUSOR HYPERCONTRACTILITY

Smooth muscle relaxants and anticholinergics (e.g., dicyclomine, oxybutynin, propantheline bromide, imipramine, flavoxate) have been used to decrease inappropriate, involuntary detrusor contractions associated with lower urinary tract inflammation, but their use should be reserved for those animals that do not respond to treatment of the primary disorder (e.g., antibiotics for bacterial urinary tract infections). Animals with chronic or recurrent cystitis require a thorough evaluation of the cause of the urinary tract infection (see Chapter 45). Antispasmodics may provide a small degree of relief; however, the identification and elimination of the underlying inflammatory disorder should be the priority. When the detrusor hypercontractility is primary or idiopathic, anticholingeric agents may be beneficial.

### **CONGENITAL DISORDERS**

The correction of congenital defects depends on the nature and extent of the defect. For example, a patent urachus or urachal diverticulum is surgically correctable, as are many forms of ectopic ureters. However, because USMI may occur in conjunction with an ectopic ureter, surgical reimplantation of the ureter does not guarantee continence. The use of  $\alpha$ -adrenergic drugs after surgery increases the likelihood of success. Urethral pressure profilometry can be used to detect USMI and measure the response to  $\alpha$ -adrenergic drugs before surgery.

### ANATOMIC URETHRAL OBSTRUCTION

In animals with an anatomic urethral obstruction, the size and nature of the lesion can usually be determined by retrograde positive-contrast urethrography. The prevention of renal damage secondary to urinary obstruction and the relief of urinary obstruction to prevent detrusor atony resulting from overdistention are the main priorities in dogs and cats with urine outflow tract obstructions. If the obstruction is created by a urethral urolith, retropulsion of the urolith into the bladder may be successful. If the urolith cannot be moved by retropulsion, a temporary or permanent perineal urethrostomy may be necessary.

In dogs with benign prostatic hyperplasia resulting in urethral obstruction, castration usually leads to a rapid decrease in the size of the prostate. The use of estrogens to decrease prostatic size is not recommended because of the potential for systemic adverse effects and the development of squamous metaplasia of the prostate. Surgical drainage and marsupialization may be necessary to manage prostatic abscesses or prostatic cysts. In some cases of prostatic neo-

plasia, partial or complete prostatectomy or radiotherapy may be beneficial; however, prostatectomy is difficult and frequently results in neurologic damage and USMI.

### **Prognosis**

In general, the prognosis for animals with neurogenic forms of urinary incontinence is poor. The long-term prognosis for animals with most types of spinal cord lesions is unfavorable, unless an intervertebral disk protrusion can be successfully decompressed or an extradural mass successfully removed or treated with chemotherapy or radiotherapy. Even if the spinal cord is decompressed, normal micturition may not completely return because the central nervous system has a minimal capacity for regeneration. Damage to the pudendal nerve, pelvic nerve, or sacral nerve roots is associated with a more favorable prognosis because peripheral nerves have a greater capacity to regenerate.

Most of the time, reflex dyssynergia responds to pharmacologic management, but occasionally the underlying disease worsens, making pharmacologic management ineffective. Drug doses should be reevaluated and increased if this happens, but this is not always successful. Diagnostic procedures such as myelography, an epidurography, CT, or magnetic resonance imaging (MRI) may be indicated in these refractory cases. Catheterization using aseptic techniques may be necessary for the long-term management of these animals.

Periodic urinalyses to identify or rule out urinary tract infections constitute an important aspect of follow-up care in an animal with any disorder of micturition. The frequency of the urinalyses depends on the nature of the disorder. Owners can be instructed to evaluate the color and odor of the urinc and to bring in a urine sample immediately if they suspect an infection; however, routine monitoring is the cornerstone of the prevention of severe urinary tract infections. The prognosis for animals with USMI is usually good, although some dogs require multiple drugs for management.

Dogs treated for urge or inflammatory incontinence secondary to a urinary tract infection should undergo follow-up urinalysis or urine bacterial culture studies to confirm that the urinary tract infection has been eliminated. Long-term dietary management may help prevent recurrences in animals with urolithiasis.

The prognosis for dogs and cats with trigonal or urethral neoplasia is usually poor. In most cases, urethral neoplasia is inoperable because the clinical signs (dysuria, stranguria, hematuria, urethral obstruction) are usually not observed until the tumor is invasive. In contrast, most female dogs with granulomatous (chronic active) urethritis respond well to a combination of prednisolone, cyclophosphamide, and antibiotics.

### Suggested Readings

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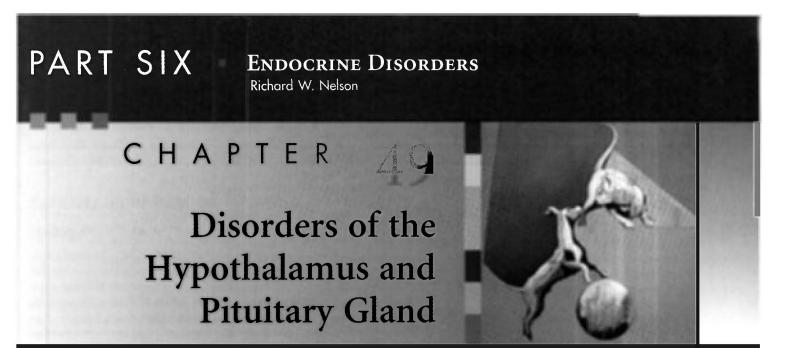
# Drugs Used in Dogs and Cats with Urinary Tract Disorders

DRUG	TRADE NAME	ACTION	DOSE
Allopurinol	Zyloprim	Xanthine oxidase inhibitor	10 mg/kg q8-24h PO (dog)
Aluminum carbonate, aluminum hydroxide	Basal gel, Amphojel	Enteric phosphate binders	10-30 mg/kg q8h PO with or immediately after meals
Amitriptyline	Elavil Anticholinergic effect decreased histami release from mast increased bladder compliance		5-10 mg q24h (evening) PO (cat)
Amlodipine	Norvasc	Calcium antagonist	2.5 mg q24h (dog); 0.625 mg q24h (cat)
Ammonium chloride		Urinary acidifier	100 mg/kg q12h PO (dog); 800 mg mixed with food daily (approximately 1/4 tsp) (cat)
Aspirin		Antiplatelet, anti- inflammatory	0.5-5 mg/kg q12h (dog); 0.5-5 mg/kg q24h (cat)
Azathioprine	lmuran	Immunosuppressant	1-2 mg/kg PO q24h initially, then 0.5- 1.0 mg/kg PO q48h (dogs only)
Benazepril	Lotensin	Angiotensin-converting enzyme inhibitor	0.25-0.5 mg/kg PO q24h
Bethanechol	Urecholine	Cholinergic (increases detrusor contractility)	5-15 mg q8h PO (dog); 1.25-5 mg q8h PO (cat)
Chlorpromazine	Thorazine	Antiemetic	0.25-0.5 mg/kg q6-8h IM, SQ, PO (after rehydration only)
Cimetidine	Tagamet	H <sub>2</sub> blocker	2.5-5.0 mg/kg q12h PO, IV, IM
Cyclophosphamide	Cytoxan, Neosar	Immunosuppressant	50 mg/m <sup>2</sup> PO q48h (dogs); 200-300 mg/ m <sup>2</sup> PO q3wk (cats)
Cyclosporine	Neoral, Sandimmune	Immunosuppressant	3-7 mg/kg q12-24h, adjust dose via monitoring
Diazepam	Valium	Skeletal muscle relaxant	2-5 mg q8h PO

Drugs Used in Dogs and Cats with Urinary Tract Disorders—cont'd

DRUG	TRADE NAME	ACTION	DOSE
Dicyclomine	Bentyl, Bentylol	Antispasmodic, antimuscarinic	0.15 mg/kg PO q8-12h (dog)
Diethylstilbestrol (DES)		Increased urethral sphincter tone	0.1-1.0 mg q24h PO for 3-5 days and then same dose q3-7days (dog); 0.05- 0.1 mg q24h PO q3-5days and then same dose q3-7days (cat)
1,25-Dihydroxychole- calciferol, calcitriol	Rocaltrol	Active vitamin D <sub>3</sub> , decreases parathyroid hormone	1.5-3.5 ng/kg q24h PO
Enalapril	Enacard	Angiotensin-converting enzyme inhibitor	0.5 mg/kg q12-24h PO (dog); 0.25- 0.5 mg/kg q12-24h PO (cat)
Ephedrine		α-Adrénergic, increases urethral sphincter tone	12.5-50 mg q12h PO (dog); 2-4 mg/kg q8-12h PO (cat)
Erythropoietin (r-Hu- EPO), epoetin alfa	Epogen	Stimulate erythrogenesis	35-50 U/kg IV, SQ 3 times/wk or 400 U/kg IV, SQ weekly; adjust dose to PCV of 30%-35%
Famotidine	Pepcid	H <sub>2</sub> blocker	0.5 mg/kg IM, SQ, PO q12-24h
Flavoxate	Urispas	Muscle relaxant	100-200 mg q6-8h
Furosemide	Lasix	Loop diuretic	2-4 mg/kg q8-12h iV, PO
Hydralazine	Apresoline	Arterial vasodilator	0.5-2.0 mg/kg q12h PO (dog); 2.5 mg q24h-q12h PO (cat)
Imipramine	Tofranil	Antimuscarinic, adrenergic agonist, muscle relaxant	5-15 mg PO q12h (dog); 2.5-5 mg PO q12h (cat)
Lisinopril	Prinivil, Zestril	Angiotensin-converting enzyme inhibitor	0.5 mg/kg PO q24h (dog)
Mannitol	Osmitrol	Osmotic diuretic	0.5-1.0 g/kg as 20%-25% solution, slow IV bolus over 5-10 min
N-(2-mercaptopropionyl)- glycine		Disulfide bond formation with cysteine	10-15 mg/kg q12h PO (dog)
Metoclopramide	Regian	Antiemetic	0.2-0.5 mg/kg q8h PO, SQ
Nandrolone decanoate	Deca-Durabolin	Anabolic steroid	1.0-1.5 mg/kg weekly IM (dog); 1.0 mg weekly IM (cat)
Oxybutynin	Ditropan	Direct antispasmodic effect on smooth muscle	0.2-0.5 mg/kg q8-12h PO (dog)
d-Penicillamine	Cuprimine	Disulfide bond formation with cysteine	10-15 mg/kg q12h PO (dog)
Phenoxybenzamine	Dibenzyline	α-Blocker, decreases urethral sphincter tone	0.2-0.5 mg/kg q24h PO (dog); 0.5 mg/kg q24h PO (cat)
Phenylpropanolamine	Propagest	α-Adrenergic, increases urethral sphincter tone	1.5-2.0 mg/kg q8-12h PO
Prazosin	Minipress	α-Blocker	1 mg/15 kg PO q6-8h
Propantheline bromide	Pro-Banthine	Anticholinergic, decreases detrusor contractility	0.25-0.5 mg/kg q8-12h PO
Racemethionine	Uroeze, Methio-Form	Urinary acidifier	150-300 mg/kg/day PO (dog); 1.0-1.5 g/ day PO (cat)
Ranitidine	Zantac	H <sub>2</sub> blocker	2.0 mg/kg q8h PO, IV (dog); 2.5 mg/kg q12h IV, 3.5 mg/kg q12h PO (cat)
Testosterone cypionate	Andro-Cyp	Increased urethral sphincter tone	1.0-2.2 mg/kg q30days IM (dog)
Trimethobenzamide	Tigan	Antiemetic	3.0 mg/kg q8h PO, IM (dog)

PCV, Packed cell volume.



### CHAPTER OUTLINE

POLYURIA AND POLYDIPSIA DIABETES INSIPIDUS

Central Diabetes Insipidus
Nephrogenic Diabetes Insipidus
Signalment
Clinical Signs
Physical Examination
Modified Water Deprivation Test
Response to Desmopressin (dDAVP)
Random Plasma Osmolality
Additional Diagnostic Tests
PRIMARY (PSYCHOGENIC) POLYDIPSIA
ENDOCRINE ALOPECIA

FELINE ACROMEGALY
Acromegaly versus Hyperadrenocorticism
PITUITARY DWARFISM

Signalment Clinical Signs

### **POLYURIA AND POLYDIPSIA**

Water consumption and urine production are controlled by complex interactions among plasma osmolality and volume, the thirst center, the kidney, the pituitary gland, and the hypothalamus. Dysfunction in any of these areas results in the clinical signs of polyuria (PU) and polydipsia (PD). In dogs normal water intake is usually less than 60 ml/kg of body weight/24 h, with an upper normal limit of 100 ml/kg. Similar values are used for cats, although most cats drink considerably less than these amounts. Normal urine output varies between 20 and 45 ml/kg/24 h. PD and PU in the dog and cat have been defined as water consumption that exceeds 100 ml/kg/24 h and urine production greater than 50 ml/

kg/24 h, respectively. It is possible, however, for thirst and urine production to be abnormal within the limits of these normal values in individual dogs and cats.

A variety of metabolic disturbances can cause PU/PD (see Box 41-3). Primary polyuric disorders can be classified on the basis of the underlying pathophysiology into primary pituitary and nephrogenic diabetes insipidus, secondary nephrogenic diabetes insipidus, osmotic diuresis-induced polyuria, and interference with the hypothalamic-pituitary secretion of arginine vasopressin (AVP). The most common form of diabetes insipidus is acquired secondary nephrogenic diabetes insipidus. This form includes a variety of renal and metabolic disorders in which the renal tubules lose the ability to respond adequately to AVP. Most of these acquired forms are potentially reversible after elimination of the underlying illness.

Secondary nephrogenic diabetes insipidus results from interference with the normal interaction of AVP and renal tubular AVP receptors, problems with the generation of intracellular cAMP, problems with renal tubular cell function, or loss of the renal medullary interstitial concentration gradient. Primary polydipsic disorders occur in dogs and usually have a psychogenic or behavioral basis for the compulsive water consumption (see the discussion of psychogenic PD, p. 702). A complete discussion of the diagnostic approach to PU/PD is presented on p. 704. An index of suspicion for most of the endocrinopathies that cause PU/PD can be raised after a review of the history, physical examination findings, and results of a complete blood count (CBC), serum biochemistry panel, and urinalysis. Specific tests may be necessary to confirm the diagnosis (Table 49-1). See the appropriate chapters in this section for a more complete discussion of the diagnosis and treatment of each of these endocrinopathies.

Occasionally, the physical examination findings and initial blood and urine tests are normal in dogs and cats with PU and PD. Differential diagnoses in these dogs and cats include diabetes insipidus, psychogenic PD, hyperadrenocorticism,



# Endocrine Disorders Causing Polyuria and Polydipsia in the Dog and Cat

TESTS TO ESTABLISH THE DIAGNOSIS		
Fasting blood glucose, urinalysis		
Urine C/C ratio, low-dose dexamethasone suppression test		
Blood electrolytes, ACTH stimulation test		
Blood calcium/phosphorus, cervical ultrasound, serum PTH concentration		
Serum T₄ and free T₄ concentration		
Modified water deprivation test, response to dDAVP therapy		
' ' '		
Baseline GH or IGF-I concentration, CT or MR scan		
Blood electrolytes, plasma aldosterone concentration		

C/C, Cortisol/creatinine; ACTH, Adrenocorticotropic hormone; PTH, parathyroid hormone; GH, growth hormone; IGF-I, Insulin-like growth factor-I; CT, computed tomographic; MR, magnetic resonance.



**TABLE 49-2** 

Results of Urinalysis in Dogs with Selected Disorders Causing Polyuria and Polydipsia

			NE SPECIFIC BRAVITY	2027DUDIA	Mana C E (LIDE)	D.A. CTERMINIA
DISORDER	NO. OF DOGS	MEAN	RANGE	PROTEINURIA (%)	WBC (>5/HPF) (%)	BACTERIURIA (%)
Central diabetes insipidus	20	1.005	1.001-1.012	5%	0%	0%
Psychogenic polydipsia	18	1.011	1.003-1.023	0%	0%	0%
Hyperadrenocorticism	20	1.012	1.001-1.027	48%	0%	12%
Renal insufficiency	20	1.011	1.008-1.016	90%	25%	15%
Pyelonephritis	20	1.019	1.007-1.045	70%	<i>7</i> 5%	80%

WBC, White blood cells; HPF, high-power field.

mild renal insufficiency without azotemia, and mild hepatic insufficiency, most notably with portosystemic shunts. Hyperadrenocorticism, renal insufficiency, and hepatic insufficiency should be ruled out before performing diagnostic tests for diabetes insipidus or psychogenic PD. Diagnostic tests to consider include evaluating the range of urine specific gravities obtained from several urine samples (discussed in more detail below), tests for hyperadrenocorticism (e.g., urine cortisol: creatinine ratio, low-dose dexamethasone suppression test), liver function tests (e.g., measurement of preprandial and postprandial bile acid levels), determination of the urine protein: creatinine (P/C) ratio, and abdominal ultrasonography. Ideally, all realistic causes of secondary acquired nephrogenic diabetes insipidus should be ruled out before performing tests (especially the modified water deprivation test) for primary pituitary and nephrogenic diabetes insipidus and psychogenic PD.

Critical evaluation of urine specific gravity measured from several urine samples obtained by the client at different times of the day for 2 to 3 days may provide clues to the underlying disorder (Table 49-2). Urine samples should be stored in the refrigerator until they can be brought to the

veterinary hospital for determination of urine specific gravity. Urine specific gravity varies widely among healthy dogs and can range from 1.006 to greater than 1.040 within a 24-hour period. Wide fluctuations in urine specific gravity have not been reported in healthy cats. If the urine specific gravity is consistently in the isosthenuric range (1.008 to 1.015), renal insufficiency should be considered the primary differential diagnosis, especially if the blood urea nitrogen and serum creatinine concentration are high normal or increased (i.e., 25 mg/dl or more and 1.6 mg/dl or more, respectively). Isosthenuria is relatively common in dogs with hyperadrenocorticism, psychogenic water consumption, hepatic insufficiency, pyelonephritis, and partial diabetes insipidus with concurrent water restriction, but urine specific gravities above (e.g., hyperadrenocorticism, pyelonephritis, hepatic insufficiency, psychogenic water consumption) or below (e.g., hyperadrenocorticism, hepatic insufficiency, partial diabetes insipidus) the isosthenuric range also occur with these disorders. If urine specific gravities less than 1.005 (i.e., hyposthenuric) are identified, renal insufficiency and pyelonephritis are ruled out and diabetes insipidus, psychogenic water consumption, hyperadrenocorticism, and hepatic insufficiency should be considered. Primary pituitary and nephrogenic diabetes insipidus are ruled out if the urine specific gravity exceeds 1.020. Urine specific gravities that range from less than 1.005 to greater than 1.030 are suggestive of psychogenic PD.

# **DIABETES INSIPIDUS**

# Etiology

AVP plays a key role in the control of renal water resorption, urine production and concentration, and water balance. AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus, is stored in and secreted from the posterior pituitary gland in response to an increase in plasma osmolality or decrease in extracellular fluid volume, and interacts with distal tubular and collecting duct cells of the kidney to promote water resorption and the formation of concentrated urine. The defective synthesis or secretion of AVP or an inability of the renal tubules to respond to AVP causes diabetes insipidus.

#### CENTRAL DIABETES INSIPIDUS

Central diabetes insipidus (CDI) is a polyuric syndrome that results from insufficient secretion of AVP to concentrate urine for water conservation. This deficiency may be absolute or partial. An absolute deficiency of AVP, referred to as complete CDI, causes persistent hyposthenuria and severe diuresis. The urine specific gravity in dogs and cats with complete CDI remains hyposthenuric (i.e., 1.005 or less), even with severe dehydration. A partial deficiency of AVP, referred to as partial CDI, also causes persistent hyposthenuria and a marked diuresis as long as the dog or cat has unlimited access to water. During periods of water restriction the urine specific gravity can increase into the isosthenuric range (i.e., 1.008 to 1.015), but typically the urine cannot be concentrated to more than 1.015 to 1.020 even when the animal is severely dehydrated. In any dog or cat with partial CDI the maximum urine-concentrating ability during dehydration is inversely related to the severity of the deficiency in AVP secretion—that is, the more severe the AVP deficiency, the less concentrated the urine specific gravity during dehydration.

CDI may result from any condition that damages the neurohypophyseal system (Box 49-1). Idiopathic CDI is the most common form, appearing at any age, in any breed, and affecting animals of either sex. Necropsies performed in dogs and cats with idiopathic CDI fail to identify an underlying reason for the AVP deficiency. Although CDI is well documented in kittens and puppies, a hereditary form of CDI has not yet been documented. The most common identifiable causes of CDI in dogs and cats are head trauma (accidental or neurosurgical), neoplasia, and hypothalamic-pituitary malformations (e.g., cystic structures). Head trauma may cause a transient (typically lasting 1 to 3 weeks) or permanent CDI, depending on the viability of the cells in the supraoptic and paraventricular nuclei.



Recognized Causes of Diabetes Insipidus in Dogs and Cats

CENTRAL DIABETES INSIPIDUS	NEPHROGENIC DIABETES INSIPIDUS
Idiopathic Traumatic Neoplasia Craniopharyngioma Chromophobe adenoma Chromophobe adenocarcinoma Metastasis Hypothalamic and pituitary malformation Cysts Inflammation Familial (?)	Primary idiopathic Primary familial (Huskies) Secondary acquired (see Box 41-4)

Primary intracranial tumors that are associated with diabetes insipidus in dogs and cats include craniopharyngioma, pituitary chromophobe adenoma, and pituitary chromophobe adenocarcinoma. Metastatic mammary carcinoma, lymphoma, malignant melanoma, and pancreatic carcinoma have been reported to cause CDI in dogs through their presence in the pituitary gland or hypothalamus. Metastatic neoplasia has not yet been reported to be a cause of CDI in cats.

#### **NEPHROGENIC DIABETES INSIPIDUS**

Nephrogenic diabetes insipidus (NDI) is a polyuric disorder that results from impaired responsiveness of the nephron to AVP. Plasma AVP concentrations are normal or increased in animals with this disorder. NDI is classified as either primary (familial) or secondary (acquired). Primary NDI is a rare congenital disorder in dogs and cats, with only a few reports in the literature. The etiology of primary NDI in dogs and cats is unknown, although decreased binding affinity of AVP receptors was identified in a family of Siberian Huskies. Affected puppies showed antidiuretic responses to high doses of synthetic vasopressin (desmopressin [dDAVP]).

# **Clinical Features**

#### SIGNALMENT

There is no apparent breed-, sex-, or age-related predilection for CDI. In one study the age at the time of the diagnosis of CDI in dogs ranged from 7 weeks to 14 years, with a median of 5 years. Similarly, most cats with CDI are domestic short- and long-haired cats, although the disorder has also been documented in Persians and Abyssinians. The age at the time of diagnosis of CDI in cats ranged from 8 weeks to 6 years, with a mean of 1.5 years. Primary NDI has been identified only in puppies, kittens, and young adult dogs and cats

younger than 18 months of age. PU and PD have been present since the clients acquired these pets.

#### **CLINICAL SIGNS**

PU and PD are the hallmark signs of diabetes insipidus and are typically the only signs seen in dogs and cats with congenital and idiopathic CDI and in those with primary NDI. Clients may believe that affected animals are incontinent because of the frequency of urination and loss of normal housebroken behavior. Owners of cats with diabetes insipidus often complain that they need to change the kitty litter more frequently than expected. Additional clinical signs may be found in dogs and cats with secondary causes of diabetes insipidus. The most worrisome are neurologic signs, which may indicate the presence of an expanding hypothalamic or pituitary tumor in the adult dog or cat that has not had head trauma.

# PHYSICAL EXAMINATION

The physical examination findings are usually unremarkable in animals with CDI, although some dogs and cats are thin, presumably because the pet's strong desire for water overrides its normal appetite. As long as access to water is not restricted, the animal's hydration status, mucous membrane color, and capillary refill time remain normal. The presence of neurologic abnormalities is variable in dogs and cats with either trauma-induced CDI or neoplastic destruction of the hypothalamus or pituitary gland. When present, neurologic signs may include stupor, disorientation, ataxia, circling, pacing, and convulsions. Severe hypernatremia may also cause neurologic signs in the traumatized dog or cat with undiagnosed CDI given inadequate fluid therapy (see

Chapter 55). Hyposthenuria in the presence of persistent hypernatremia should raise suspicion for diabetes insipidus.

# **Diagnosis**

The diagnostic workup for PU and PD should initially rule out causes of acquired secondary NDI (see Chapter 41). Recommended initial diagnostic studies include a CBC; biochemistry panel; urinalysis with bacterial culture; abdominal ultrasonography; and a urine cortisol: creatinine ratio, low-dose dexamethasone suppression test, or both. Results of these screening tests are normal in dogs and cats with CDI, primary NDI, and psychogenic water consumption, although a low-normal serum urea nitrogen concentration (5 to 10 mg/dl) may be found. Random urine specific gravity is usually less than 1.006 and is often as low as 1.001 if the dog or cat has unlimited access to water. The urine osmolality is less than 300 mOsm/kg. A urine specific gravity in the isosthenuric range (i.e., 1.008 to 1.015) does not rule out diabetes insipidus (Fig. 49-1), especially if the urine has been obtained after water is knowingly or inadvertently withheld (e.g., a long car ride and wait in the veterinary office). The urine of dogs and cats with partial diabetes insipidus can be concentrated into the isosthenuric range if they are dehydrated. Erythrocytosis (packed cell volume of 50% to 60%), hyperproteinemia, hypernatremia, and azotemia may be found in animals if their access to water has been restricted.

Diagnostic tests to confirm and differentiate among CDI, primary NDI, and psychogenic water consumption include the modified water deprivation test, random plasma osmolality determination, and the response to AVP supplementation. The results of these tests can be interpreted only after

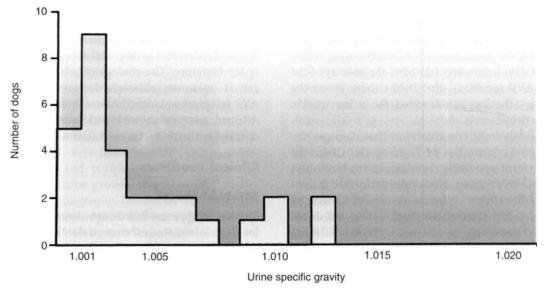


FIG 49-1
Urine specific gravity measured in 30 dogs with central diabetes insipidus at the time of initial presentation to the veterinarian. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

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the causes for acquired secondary NDI have been ruled out.

#### MODIFIED WATER DEPRIVATION TEST

The technique, interpretation, contraindications, and complications of the modified water deprivation test are described in Chapter 42. The test consists of two phases. In phase I the AVP secretory capabilities and renal distal and collecting tubule responsiveness to AVP are evaluated by assessing the effects of dehydration (i.e., water restriction until the animal loses 3% to 5% of its body weight) on urine specific gravity. The normal dog and cat, as well as those with psychogenic water consumption, should be able to concentrate urine to greater than 1.030 (1.035 in the cat) if dehydrated. Dogs and cats with partial and complete CDI and primary NDI have an impaired ability to concentrate urine in the face of dehydration (Table 49-3 and Fig. 49-2). The time required to attain 3% to 5% dehydration can sometimes be helpful in establishing the diagnosis. It often takes less than 6 hours for dogs and cats with complete CDI to attain 3% to 5% dehydration, whereas it often takes more than 8 to 10 hours for dogs and cats with partial CDI, and especially those with psychogenic water consumption, to attain 3% to 5% dehydration.

Phase II of the water deprivation test is indicated for dogs and cats that do not concentrate urine to greater than 1.030 during phase I of the test. Phase II determines the effect, if any, that exogenous AVP has on the renal tubular ability to concentrate urine in the face of dehydration (see Fig. 49-2). This phase differentiates impaired AVP secretion from impaired renal tubular responsiveness to AVP (see Table 49-3).

# **RESPONSE TO DESMOPRESSIN (dDAVP)**

An alternative approach to establishing the diagnosis is to evaluate the animal's response to trial therapy with dDAVP (desmopressin acetate, Aventis Pharmaceuticals). One 0.1-mg or one-half of a 0.2-mg (dog) and one-half of a 0.1-mg (cat) dDAVP tablet is administered orally every 8 hours, or 1 to 4 drops of dDAVP nasal spray is administered from an eye dropper into the conjunctival sac every 12 hours for 5 to 7 days. The effect of dDAVP should not be critically evaluated until after 5 to 7 days of therapy because renal medul-

lary solute washout may prevent a dog or cat with CDI from forming concentrated urine in response to only one or two administrations. Clients should notice a decrease in PU and PD by the end of the treatment period if the PU and PD are caused by CDI. Urine specific gravity should be measured

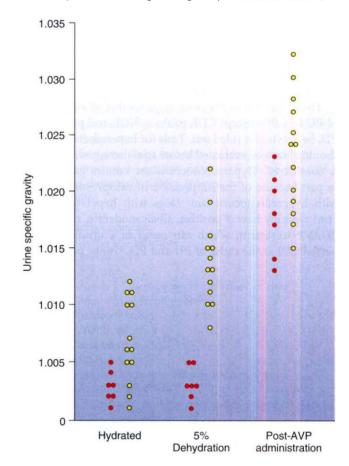


FIG 49-2

Urine specific gravity in seven dogs with complete central diabetes insipidus (red circle) and 13 dogs with partial central diabetes insipidus (yellow circle) at the beginning (hydrated), end of phase I (5% hydrated), and end of phase II (after arginine vasopressin administration) of the modified water deprivation test. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)



TABLE 49-3

Guidelines for Interpretation of the Modified Water Deprivation Test

	URINE SPECIFIC GRAVITY			TIME TO 5% DEHYDRATION	
DISORDER	INITIALLY	5% DEHYDRATION	POST ADH	MEAN (hr)	RANGE (hr)
Central DI					
Complete	<1.006	<1.006	>1.008	4	3-7
Partial	<1.006	1.008-1.020	>1.015	8	6-11
Primary nephrogenic DI	<1.006	<1.006	<1.006	5	3-9
Primary polydipsia	1.002-1.020	>1.030	NA	13	8-20

on several urine samples collected by the client on the last couple of days of trial therapy. An increase in urine specific gravity by 50% or more, compared with pretreatment specific gravities, supports the diagnosis of CDI, especially if the urine specific gravity exceeds 1.030. There should be only minimal improvement in dogs and cats with primary NDI, although a response may be observed with very high doses of dDAVP. Dogs and cats with psychogenic water consumption may exhibit a mild decline in urine output and water intake because the chronically low serum osmolality tends to depress AVP production.

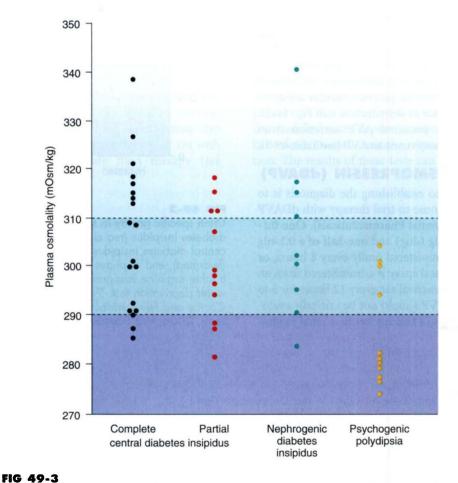
This approach to diagnosis requires that all other causes of PU and PD, except CDI, primary NDI, and psychogenic PD, be previously ruled out. Tests for hyperadrenocorticism should always be evaluated before trial therapy with dDAVP is considered. Hyperadrenocorticism mimics partial CDI, in part because of the suppression of vasopressin secretion with hyperadrenocorticism. Dogs with hyperadrenocorticism typically have a positive, albeit moderate, response to dDAVP treatment, which can result in a misdiagnosis of partial CDI as the cause of PU and PD. Unlike partial CDI,

the beneficial response to dDAVP wanes over the ensuing weeks in dogs with hyperadrenocorticism.

Although less time-consuming than the water deprivation test, the expense is often comparable, in part because of the cost of the dDAVP. In addition, the modified water deprivation test may still have to be performed if ambiguous results are obtained using this simpler approach.

#### RANDOM PLASMA OSMOLALITY

Measurement of random plasma osmolality may help identify primary or psychogenic PD. Plasma osmolality in normal dogs and cats is approximately 280 to 310 mOsm/kg. Diabetes insipidus is a primary polyuric disorder, with compensatory PD to prevent severe hyperosmolality. Random plasma osmolality should be greater than 300 mOsm/kg. Psychogenic PD is a primary polydipsic disorder, with compensatory PU to prevent hyposmolality and water intoxication. Random plasma osmolality should be less than 280 mOsm/kg. Unfortunately, there is considerable overlap in random plasma osmolality in animals with these disorders (Fig. 49-3). A random plasma osmolality of less than 280 mOsm/kg



Random plasma osmolality in 19 dogs with complete central diabetes insipidus, 12 dogs with partial central diabetes insipidus, 9 dogs with primary nephrogenic diabetes insipidus, and 11 dogs with primary (psychogenic) polydipsia. Note the overlap in values between groups of dogs. *Dashed lines*, Upper and lower limits for normal plasma

osmolality. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

obtained while the dog or cat has free access to water suggests the presence of psychogenic PD, whereas a plasma osmolality greater than 280 mOsm/kg is consistent with CDI, NDI, or psychogenic PD.

# **ADDITIONAL DIAGNOSTIC TESTS**

Neoplasia in the region of the pituitary and hypothalamus should be considered in the older dog or cat in which CDI develops. A complete neurologic evaluation, including computed tomographic (CT) or magnetic resonance (MR) scan may be warranted before idiopathic CDI is arbitrarily diagnosed, especially if the client is willing to consider radiotherapy or chemotherapy should a tumor be identified. Similarly, a more complete evaluation of the kidney (e.g., creatinine clearance studies, intravenous pyelogram, CT or MR scan, renal biopsy) may be warranted in the older dog or cat tentatively considered to have primary NDI.

# **Treatment**

Therapeutic options for dogs and cats with diabetes insipidus are listed in Box 49-2. The synthetic analog of vasopressin, dDAVP, is the standard therapy for CDI. dDAVP has almost three times the antidiuretic action of AVP, with minimal-to-no vasopressor or oxytocic activity. The intranasal dDAVP preparation (dDAVP nasal drops, 2.5- and 5.0-ml bottles containing 100 µg dDAVP/ml) is used most commonly for treating CDI in dogs and cats. Administration of medication to animals via the intranasal route is possible but not recommended. The dDAVP nasal preparation may be transferred to a sterile eye dropper bottle and drops placed into the conjunctival sac of the dog or cat. Although the solution is acidic, ocular irritation rarely occurs. One drop of dDAVP contains 1.5 to 4 µg of dDAVP, and a dosage of one to four drops administered once or twice daily controls signs of CDI in most animals.

Oral dDAVP (dDAVP tablets, 0.1 and 0.2 mg) can be used to treat CDI, although the clinical response is variable. The bioavailability of oral dDAVP is approximately 5% to 15% of the intranasal dose in humans. Similar information is not available for dogs and cats. The initial oral dDAVP dose is 0.1 mg (dogs) and 0.05 mg (cats) given three times a day. The dose is gradually increased to effect if unacceptable PU and PD persist 1 week after therapy is initiated. Decreasing the frequency of administration to twice a day, decreasing the dose of dDAVP, or both can be tried once clinical response has been documented. To date, most dogs have required 0.1 to 0.2 mg of dDAVP two to three times a day, and most cats have required 0.025 to 0.05 mg of dDAVP two to three times a day to control PU and PD. Treatment should be switched to the intranasal dDAVP preparation if there is minimal to no response to 0.2 mg (dog) or 0.05 mg (cat) of oral dDAVP administered three times a day.

The maximal effect of dDAVP, regardless of the route of administration, occurs from 2 to 8 hours after administration, and the duration of action varies from 8 to 24 hours. Larger doses of dDAVP appear both to increase its antidiuretic effects and to prolong its duration of action; however,



BOX 49-2

Therapies Available for Polydipsic/Polyuric Dogs and Cats with Central Diabetes Insipidus, Nephrogenic Diabetes Insipidus, or Primary (Psychogenic) Polydipsia

- A. Central diabetes insipidus (severe)
  - 1. dDAVP (desmopressin acetate)
    - a. Effective
    - b. Expensive
    - C. Oral tablets or drops of nasal solution in conjunctival sac
  - 2. LVP (lypressin [Diapid])
    - a. Short duration of action; less potent than dDAVP
    - b. Expensive
    - c. Requires drops into nose or conjunctival sac
  - 3. No treatment-provide continuous source of water
- B. Central diabetes insipidus (partial)
  - dDAVP
  - LVP
  - 3. Chlorpropamide
    - a. 30%-70% effective
    - b. Inexpensive
    - c. Pill form
    - d. Takes 1-2 weeks to obtain effect of drug
    - e. May cause hypoglycemia
  - 4. Thiazide diuretics
    - a. Mildly effective
    - b. Inexpensive
    - c. Pill form
    - d. Should be used with low-sodium diet
  - 5. Low-sodium diet (NaCl < 0.9 g/1000 kcal/ME)
  - 6. No treatment-provide continuous source of water
- C. Nephrogenic diabetes insipidus
  - 1. Thiazide diuretics
  - 2. Low-sodium diet (NaCl < 0.9 g/1000 kcal/ME)
  - 3. No treatment-provide continuous source of water
- D. Primary (psychogenic) polydipsia
  - 1. Water restriction at times
  - 2. Water limitation
  - 3. Change in environment or daily routine; excercise; increased contact with humans or dogs

ME, Metabolizable energy

expense becomes a limiting factor. The medication may be administered exclusively in the evening as insurance against nocturia.

Chlorpropamide, thiazide diuretics, and oral sodium chloride restriction have a limited efficacy in the treatment of NDI. dDAVP may control the clinical signs if administered in massive amounts (i.e., five to ten times the amount used for the treatment of CDI), but the cost of the drug obviously detracts from the attractiveness of this therapeutic approach. Fortunately, therapy for CDI or NDI is not mandatory as long as the dog or cat has unlimited access to water and is housed in an environment that cannot be damaged by severe PU. A constant water supply is of paramount importance because relatively short periods of water restric-

tion can have catastrophic results (i.e., the development of hypernatremic, hypertonic dehydration and neurologic signs).

# **Prognosis**

Dogs and cats with idiopathic or congenital CDI become relatively asymptomatic in response to appropriate therapy, and with proper care these animals have an excellent life expectancy. PU and PD frequently resolve in dogs and cats with trauma-induced CDI, often within 2 weeks of the traumatic incident. The prognosis in dogs and cats with hypothalamic and pituitary tumors is guarded to grave. Neurologic signs typically develop within 6 months after the diagnosis of CDI, and clinical response to radiotherapy and chemotherapy is variable and unpredictable.

The prognosis for animals with primary NDI is guarded to poor because of limited therapeutic options and the generally poor response to therapy. The prognosis for animals with secondary NDI depends on the prognosis of the primary problem.

# PRIMARY (PSYCHOGENIC) POLYDIPSIA

Primary PD is defined as a marked increase in water intake that cannot be explained as a compensatory mechanism for excessive fluid loss. In humans primary PD results from a defect in the thirst center or may be associated with mental illness. Primary dysfunction of the thirst center resulting in compulsive water consumption has not been reported in the dog or cat, although an abnormal vasopressin response to hypertonic saline infusion has been reported in dogs with suspected primary PD. A psychogenic or behavioral basis for compulsive water consumption does occur in the dog but has not been reported in the cat. Psychogenic PD may be induced by concurrent disease (e.g., hepatic insufficiency, hyperthyroidism) or may represent a learned behavior following a change in the pet's environment. PU is compensatory to prevent overhydration.

Dogs (and presumably cats) with primary or psychogenic PD have an intact hypothalamic-pituitary-renal axis for controlling fluid balance and variable severity of renal medullary solute washout. Because AVP production and renal tubular response to AVP are normal, these dogs can concentrate urine in excess of 1.030. Depending on the severity of renal medullary solute washout, a period of 24 hours or longer of water deprivation may be necessary to attain concentrated urine. Psychogenic PD is diagnosed by exclusion of other causes of PU and PD and by demonstrating that the dog or cat can concentrate urine to a specific gravity in excess of 1.030 during water deprivation.

Treatment is aimed at gradually limiting water intake to amounts in the high-normal range. The client should determine the dog's approximate water intake in a 24-hour period when free-choice water is allowed, and this volume of water is then reduced by 10% per week until water volumes of 60 to 80 ml/kg/24 h are reached. The total 24-hour volume of

water should be divided into several aliquots, with the last aliquot given at bedtime. Oral salt (1 g/30 kg q12h) and/or oral sodium bicarbonate (0.6 g/30 kg q12h) may also be administered for 3 to 5 days to help reestablish the renal medullary concentration gradient. Changes in the dog's environment or daily routine should be considered, such as initiating a daily exercise routine; bringing a second pet into the home; providing some distraction, such as a radio playing when the clients are not home; or moving the dog to an area with an increased amount of contact with humans.

# **ENDOCRINE ALOPECIA**

Symmetric alopecia without historical or clinical evidence of inflammation usually results from hair cycle arrest induced by hormonal diseases—hence the term *endocrine alopecia* (Fig. 49-4). Hair follicles are atrophic, hairs are easily epilated, the skin is often thin and hypotonic, and hyperpigmentation is common. Other dermatologic lesions, such as scales, crusts, and papules, are absent. Seborrhea and pyoderma may develop, depending on the underlying cause.

Causes of endocrine alopecia are listed in Table 49-4. In dogs the most common causes are hypothyroidism and glucocorticoid excess (iatrogenic or spontaneous). Feline endocrine alopecia is perhaps the most common endocrine alopecia in cats. The diagnostic evaluation for endocrine alopecia begins with a complete history, physical examination, and routine blood and urine tests, (i.e., CBC, serum biochemistry panel, and urinalysis). Results of these tests will often provide evidence for hypothyroidism and hyperadrenocorticism, and appropriate diagnostic tests can then be performed to confirm these diagnoses (see Chapters 51 and 53, respectively).



FIG 40.4

Endocrine alopecia, thin skin, and severe obesity in a 7-year-old male castrated Pomeranian with iatrogenic hyperadrenocorticism caused by chronic administration of prednisone for a seizure disorder. Note the symmetric truncal alopecia with sparing of the head and distal extremities.



# Disorders Causing Endocrine Alopecia

DISORDER	COMMON CLINICOPATHOLOGIC ABNORMALITIES	DIAGNOSTIC TESTS
Hypothyroidism	Lipemia, hypercholesterolemia, mild nonregenerative anemia	Serum T <sub>4</sub> , free T <sub>4</sub> , TSH concentrations
Hyperadrenocorticism	Stress leukogram, increased ALP, hypercholesterolemia, hyposthenuria, proteinuria, urinary tract infection	Urine cortisol/creatinine ratio, low-dose dexamethasone suppression test, abdominal US
Hyperestrogenism	, , , , , , , , , , , , , , , , , , , ,	
Functional Sertoli cell tumor in male dog	None (bone marrow depression uncommon)	Physical findings, abdominal US, cytologic or histopathologic findings, plasma estrogen concentration
Hyperestrogenism in intact female dog	None (bone marrow depression uncommon)	Vaginal cytology, abdominal US, plasma estrogen concentration, response to ovariohysterectomy
Hyperprogesteronism	None	Physical findings, abdominal US, serum progesterone concentration
Increased adrenocortical steroid hormone intermediates (adrenal hyperplasia-like syndrome, Alopecia-X)	None	Measure adrenocortical steroid hormone intermediates before and after ACTH administration
Growth hormone deficiency pituitary dwarfism	None	Signalment, physical findings, growth hormone response test
Growth hormone-responsive dermatosis—adult dog	None	Growth hormone response test, response to growth hormone replacement therapy
Castration-responsive dermatosis Hypoestrogenism (?)	None	Response to castration
Estrogen-responsive dermatosis of spayed female dogs Hypoandrogenism (?)	None	Response to estrogen therapy
Testosterone-responsive dermatosis—male dog	None	Response to testosterone therapy
Feline endocrine alopecia	None	Response to progestin therapy
Telogen defluxion (effluvium)	None	History of recent pregnancy or diestrus
Diabetes mellitus	Hyperglycemia, glycosuria	Blood and urine glucose measurement

T<sub>4</sub>, Tetraiodothyronine; TSH, thyroid-stimulating hormone; ALP, alkaline phosphatase; US, ultrasonography; ACTH, adrenocorticotropic hormone.

Once hypothyroidism and hyperadrenocorticism have been ruled out, the next diagnostic step is to rule out an excess of one of the sex hormones or one of the adrenocortical steroid hormone intermediates. Dermatologic manifestations are similar for most sex hormone—induced dermatoses and include endocrine alopecia that initially begins in the perineal, genital, and ventral abdominal regions and spreads cranially; dull, dry, easily epilated hair; failure of the haircoat to regrow after clipping; and variable presence of seborrhea and hyperpigmentation. Additional clinical signs of hyperestrogenism may include gynecomastia, a pendulous prepuce, the attraction of other male dogs, squatting to urinate, and unilateral testicular atrophy (contralateral to the testicular tumor) in the male dog and vulvar enlargement and persistent proestrus or estrus in the bitch. Results

of a CBC may reveal aplastic anemia. Histologic assessment of a skin biopsy specimen can be used to identify nonspecific endocrine-related alterations and support the diagnosis of endocrine alopecia (Table 49-5). There are no pathognomonic histologic changes for sex hormone—induced dermatoses. The identification of an increased plasma estrogen (i.e., estradiol) concentration would support the presence of a functional Sertoli cell tumor in the dog and hyperestrogenism in the bitch (assuming that the bitch is not in proestrus or early estrus). Abdominal ultrasound may identify ovarian cysts or neoplasia in the bitch with hyperestrogenism, and abdominal and testicular ultrasound may identify testicular neoplasia in the male dog. Hyperestrogenism and endocrine alopecia will resolve after surgical removal of the ovarian cyst, ovarian tumor, or testicular tumor.



# **TABLE 49-5**

# Dermatohistopathologic Alterations Associated with Endocrinopathy-Induced Alopecia

ABNORMALITY	SPECIFIC ENDOCRINE DISORDER
Nonspecific Abnormalities Supporting an Endocrinopathy	
Orthokeratotic hyperkeratosis	
Follicular keratosis	
Follicular dilatation	
Follicular atrophy	
Predominance of telogen hair follicles	
Sebaceous gland atrophy	The property of the property o
Epidermal atrophy	
Epidermal melanosis	And the second of the second o
Thin dermis	
Dermal collagen atrophy	THE STATE OF THE S
Abnormalities Suggestive of Specific Endocrine Disorder	
Decreased amount and size of dermal elastin fibers	Hyposomatotropism
Excessive trichilemmal keratinization (flame follicles)	Growth hormone- and castration-responsive dermatosis
Vacuolated and/or hypertrophied arrector pilae muscles	Hypothyroidism
Increased dermal mucin content	Hypothyroidism
Thick dermis	Hypothyroidism
Comedones	Hyperadrenocorticism
Calcinosis cutis	Hyperadrenocorticism
Absence of arrector pilae muscles	Hyperadrenocorticism

An abnormal increase in serum progesterone may result from adrenocortical neoplasia, functional ovarian luteal cysts in the bitch, and as a component of an imbalance in adrenocortical steroid hormone intermediates. Functional luteal cysts may cause prolonged anestrus or failure to cycle in the bitch. Clinical features of progesterone-secreting adrenocortical tumors mimic hyperadrenocorticism (see Chapter 53). Documenting increased serum progesterone concentration establishes the diagnosis, especially in a male or female spayed animal. Serum progesterone is normally increased in an intact female dog or cat in diestrus. A history of recent cycling behavior and examination of the ovaries and adrenal glands with abdominal ultrasound will help differentiate diestrus, functional luteal cysts, and adrenal neoplasia.

An increase in one or more of the adrenocortical steroid hormone intermediates often occurs in association with pituitary-dependent and adrenocortical tumor—dependent hyperadrenocorticism (Fig. 49-5). The predominant clinical signs in these dogs result from an excess of cortisol. An imbalance of adrenocortical steroid hormone intermediates such as 17-hydroxyprogesterone, progesterone, and androstenedione has been proposed as an explanation for hair cycle arrest, endocrine alopecia, and hyperpigmentation in dogs that do not have hyperadrenocorticism. A partial deficiency of 21-hydroxylase enzyme may account for the clinical and hormonal findings. Clinical signs for this syndrome (referred to as *adrenal hyperplasia-like syndrome* or *Alopecia-X*) are characterized by hair cycle arrest; bilaterally symmetric, nonpruritic alopecia; and hyperpigmentation of



FIG 49-5
A 7-year-old Poodle mix with hyperadrenocorticism and an increase in adrenocortical steroid hormone intermediates. Clinical signs included polyuria, polydipsia, and thinning of the haircoat on the trunk and tail. Tests of the pituitary-adrenocortical axis were inconclusive, and serum 17-hydroxyprogesterone concentrations were increased.

the skin and have been identified in many breeds, most notably in the American Eskimo, Pomeranian, Chow Chow, Keeshond, Malamute, Poodle, Samoyed, and Siberian Husky (Frank et al., 2003). Males are overrepresented. Routine blood and urine test results are typically normal. Skin biopsies from affected dogs show the typical changes of endo-

crine alopecia (see Table 49-5) and may also show features of follicular dysplasia. Diagnosis requires evaluation of adrenocortical steroid hormone intermediates and sex hormones before and after adrenocorticotropic hormone (ACTH) administration (see Chapter 53). The most common abnormality is an increase in serum 17-hydroxyprogesterone concentration. Currently, the only laboratory with established normal values for intermediate and sex steroids is the Endocrinology Laboratory at the University of Tennessee, College of Veterinary Medicine, Knoxville, TN 37901-1071. Treatment has included trilostane and mitotane.

The differential diagnoses become more nebulous and the ability to establish a definitive cause of the alopecia more difficult once hypothyroidism, hyperadrenocorticism, and increased sex hormone and/or adrenocortical steroid hormone intermediates have been ruled out. Clinical manifestations of growth hormone (GH)-responsive dermatosis are similar to those described for increased adrenocortical steroid hormone intermediates (Fig. 49-6). Commonly affected breeds include Chow Chows, Pomeranians, Toy and Miniature Poodles, Keeshonds, American Water Spaniels, and Samoyeds; males are overrepresented; routine blood and urine test results are normal; and the endocrine alopecia responds to GH treatment. Unfortunately, there is no commercially available assay for measuring GH in dogs, and an effective GH product for treatment is not available for dogs.

Endocrine alopecia may result from a deficiency of one of the sex hormones, most notably estrogens or androgens, or may be responsive to treatment with one of the sex hormones (see Table 49-4). Dermatologic manifestations are similar for most sex hormone-induced and sex hormoneresponsive dermatoses and mimic the syndrome induced by alterations in sex hormone and adrenocortical steroid hormone intermediates (adrenal hyperplasia-like syndrome, Alopecia-X) and GH-responsive dermatosis, creating a difficult diagnostic challenge for the veterinarian, especially when the alopecia occurs in a breed such as the Chow Chow or Pomeranian. Diagnosis of sex hormone-deficiency or sex hormone-responsive dermatosis is based on response to treatment (Table 49-6). Castration of intact male dogs or sex hormone replacement therapy (e.g., diethylstilbestrol, methyltestosterone) in previously castrated or spayed dogs can be considered in dogs with endocrine alopecia of undetermined cause. Because of potentially serious adverse reactions to sex hormone replacement therapy, the more common causes of endocrine alopecia should always be ruled out before initiating treatment. The haircoat should improve within 3 months of the start of therapy. If there is no improvement within this time, another diagnosis should be considered.

Response to melatonin treatment (3 to 6 mg q12-24h for 6 weeks) is perhaps the most innocuous nonspecific treatment option if diagnostic options have been exhausted and



A and B, Endocrine alopecia in a 6-year-old Pomeranian with suspected adult-onset, GH-responsive dermatosis. Note the symmetric truncal alopecia with lesser involvement of the extremities and sparing of the head.



TABLE 49-6

Treatment for Sex Hormone-Induced or Sex Hormone-Responsive Endocrine Alopecia

DISORDER	PRIMARY TREATMENT	POTENTIAL ADVERSE REACTIONS TO THERAPY
Sertoli cell neoplasia	Castration	None
Castration-responsive dermatosis	Castration	None
Hyperestrogenism in the intact female dog	Ovariohysterectomy	None
Estrogen-responsive dermatosis of spayed female dogs	Diethylstilbestrol, 0.1-1.0 mg PO q24h 3 weeks per month; once responds, 0.1-1 mg q4-7 days	Aplastic anemia
Feline endocrine alopecia	Megestrol acetate, 2.5-5 mg/cat q48h until hair regrows; then 2.5-5 mg/cat q7-14 days	Adrenocortical suppression, benign mammary hypertrophy, mammary neoplasia, pyometra (female cats); infertility (male cats), diabetes mellitus
Testosterone-responsive dermatosis	Methyltestosterone, 1 mg/kg (maximum 30 mg) PO q48h until hair regrows, then q4-7 days	Aggression, hepatopathy
Telogen defluxion (effluvium)	None	None
Adrenal hyperplasia-like syndrome, Alopecia-X	Mitotane, trilostane Melatonin (see Chapter 53)	Hypoadrenocorticism

PO, By mouth.

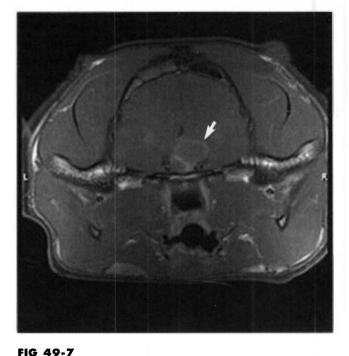
a definitive diagnosis for the endocrine alopecia has not been established. The mechanism of action of melatonin for promoting hair growth is not clear. Proposed mechanisms of action include inhibition of gonadotropin-releasing hormone (GnRH) secretion, thereby decreasing follicle-stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone concentrations; stimulation of prolactin secretion; stimulation of GH or insulin-like growth factor-I (IGF-I) secretion; and a direct effect on hair follicles.

Many clients elect not to treat their dog once hypothyroidism, hyperadrenocorticism, ovarian cysts, and neoplasia of the adrenal gland, ovary, and testis have been ruled out. For these dogs the long-term prognosis is good, even without treatment. Dogs remain healthy aside from the alopecia and hyperpigmentation.

# FELINE ACROMEGALY

#### Etiology

Chronic excessive secretion of GH in adult cats results in acromegaly, a disease characterized by overgrowth of connective tissue, bone, and viscera. In cats acromegaly is caused by a functional adenoma of the somatotropic cells of the pituitary pars distalis that secretes excess GH (Fig. 49-7). In most cats the pituitary tumor is a macroadenoma that extends dorsally above the sella turcica. Progestogen-induced acromegaly has not been documented in the cat. Progestogens, including megestrol acetate, do not appear to stimulate GH or IGF-I secretion in the cat. In contrast, acromegaly in the dog is seen most commonly after prolonged exposure to progestogens, either exogenously administered (e.g.,



Magnetic resonance image of the pituitary region of a 6-yearold male, castrated domestic short-haired cat with insulinresistant diabetes mellitus and acromegaly (see Fig. 49-8, A). A mass is evident in the hypothalamic-pituitary region (arrow).

medroxyprogesterone acetate) or late in life after years of endogenous progesterone secretion during the diestrual phase of the estrous cycle in the intact bitch.

Chronic excess secretion of GH has catabolic and anabolic effects. The anabolic effects are caused by increased concentrations of IGF-I. The growth-promoting effects of IGF-I result in proliferation of bone, cartilage, and soft tissues and in organomegaly, most notably of the kidney and heart. These anabolic effects are responsible for producing the classic clinical manifestations of acromegaly (Box 49-3). The catabolic effects of GH are a direct result of GH-induced insulin resistance that ultimately results in carbohydrate intolerance, hyperglycemia, and the development of diabetes mellitus that quickly becomes resistant to insulin treatment. Most but not all cats with acromegaly have diabetes mellitus at the time acromegaly is diagnosed, and most eventually develop severe resistance to exogenously administered insulin.

#### **Clinical Features**

Acromegaly typically occurs in male, mixed-breed cats that are 8 years of age or older. Clinical signs result from the catabolic, diabetogenic effects of GH, the anabolic actions of chronic IGF-I secretion by the liver, and growth of the pituitary macroadenoma (see Box 49-3). The earliest clinical signs are usually PU, PD, and polyphagia resulting from concurrent diabetes mellitus. Polyphagia can become quite intense. Weight loss varies and depends in part on whether the anabolic effects of IGF-I or the catabolic effects of uncontrolled diabetes predominate. Most cats initially lose weight and then experience a period of stabilization followed by a slow, progressive gain in body weight as the anabolic effects of IGF-I begin to dominate the clinical picture. Severe insulin resistance eventually develops. Insulin dosages in cats with acromegaly frequently exceed 2 to 3 U/kg of body weight twice a day, with no apparent decline in the blood glucose concentration.

Clinical signs related to the anabolic actions of excess GH secretion (see Box 49-3) may be evident at the time diabetes mellitus is diagnosed. More commonly, however, they become apparent several months after diabetes has been diagnosed, often in conjunction with the realization that hyperglycemia is difficult to control with exogenous insulin therapy. Because of the insidious onset and slowly progressive nature of the anabolic clinical signs, clients are often not aware of the subtle changes in the appearance of their cat until the clinical signs are quite obvious. Anabolic changes in acromegalic cats include an increase in body size, enlargement of the abdomen and head, development of prognathia inferior, and weight gain (Fig. 49-8). Weight gain in a cat with poorly regulated diabetes mellitus is an important diagnostic clue to acromegaly. With time, organomegaly, especially of the heart, kidney, liver, and adrenal gland, develop. Diffuse thickening of soft tissues in the pharyngeal region can lead to extrathoracic upper airway obstruction and respiratory distress.

Neurologic signs may develop as a result of pituitary tumor growth and the resultant invasion and compression of the hypothalamus and thalamus. Signs include stupor, somnolence, adipsia, anorexia, temperature deregulation, circling, seizures, and changes in behavior. Blindness is not common because the optic chiasm is located anterior to the



BOX 49-3

Clinical Signs Associated with Acromegaly in Dogs and Cats

#### Anabolic, IGF-I-Induced

Respiratory\*

Inspiratory stridor, stertor

Transient apnea

**Panting** 

Exercise intolerance

**Fatique** 

Dermatologic

Myxedema

Excessive skin folds

Hypertrichosis

Conformational\*

Increased size

Increased soft tissue in oropharyngeal/laryngeal area

Enlargement of:

Abdomen

Head\*

Feet

Viscera\*

Broad face\*

Prominent jowls\*

Prognathia inferior\*

Increased interdental space\*

Rapid toenail growth

Degenerative polyarthropathy

#### Catabolic, GH-Induced

Polyuria, polydipsia\* Polyphagia\*

# latrogenic

**Progestins** 

Mammary nodules

Pyometra

# Neoplasia-Induced

Lethargy, stupor

Adipsia

Anorexia

Temperature deregulation

Papilledema

Circling

Seizures

Pituitary dysfunction

Hypogonadism

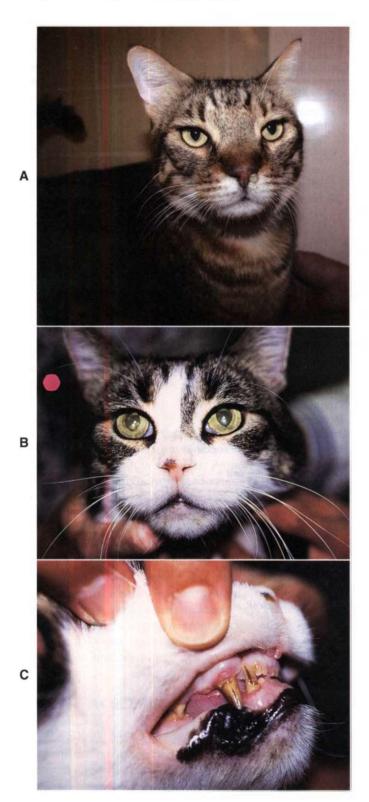
Hypothyroidism

Hypoadrenocorticism

IGF-I, Insulin-like growth factor-I; GH, growth hormone.

\* Common findings.

pituitary gland. Papilledema may be evident during an ophthalmic examination. Peripheral neuropathy causing weakness, ataxia, and a plantigrade stance may develop as a result of poorly controlled diabetes mellitus. Other endocrine and metabolic abnormalities resulting from the compressive effects of the tumor on the pituitary are uncommon.



#### FIG 49-8

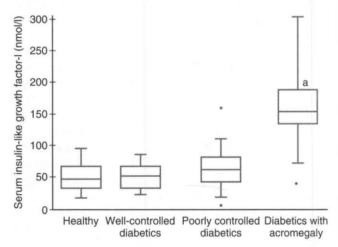
**A**, A 6-year-old male, castrated domestic short-haired cat with insulin-resistant diabetes mellitus and acromegaly. Note the broad face and mildly protruding mandible (prognathia inferior). **B** and **C**, An 8-year-old male, castrated domestic short-haired cat with insulin-resistant diabetes mellitus and acromegaly. Note the broad head, mildly protruding mandible, and prognathia inferior with displacement of the lower canine teeth. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

# **Clinical Pathology**

Concurrent, poorly controlled diabetes mellitus is responsible for causing most of the abnormalities identified on a serum biochemistry panel and urinalysis, including hyperglycemia, glycosuria, hypercholesterolemia, and a mild increase in alanine transaminase and alkaline phosphatase activities. Ketonuria is an infrequent finding. Mild erythrocytosis, persistent mild hyperphosphatemia without concurrent azotemia, and persistent hyperproteinemia (total serum protein concentration of 8.2 to 9.7 mg/dl) with a normal pattern of distribution on protein electrophoretic studies may also be found. Renal failure is a potential sequela of acromegaly and, if present, will be associated with azotemia, isosthenuria, and proteinuria.

# **Diagnosis**

Clinical suspicion for acromegaly is based on the identification of conformational alterations (e.g., increased body size, large head, prognathia inferior, organomegaly) associated with acromegaly and a stable or progressive increase in body weight in a cat with insulin-resistant diabetes mellitus. Measurement of serum IGF-I concentration provides further evidence for the diagnosis of acromegaly. Measurement of serum IGF-I is commercially available (e.g., Diagnostic Endocrinology Laboratory, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48909-7576). Concentrations are usually increased in acromegalic cats, but values may be in the reference range in the early stages of the disease (Fig. 49-9). Repeat measurements



# FIG 49-9

Box plots of serum concentrations of insulin-like growth factor-I (IGF-I) in 38 healthy cats, 15 well-controlled diabetic cats, 40 poorly controlled diabetic cats, and 19 poorly controlled diabetic cats with acromegaly. For each box plot, T-bars represent the main body of data, which in most instances is equal to the range. Each box represents the interquartile range (twenty-fifth to seventy-fifth percentile). The horizontal bar in each box is the median. Asterisks represent outlying data points. (a) P < 0.0001, compared with healthy cats and well-controlled and poorly controlled diabetic cats. (From Berg RIM et al: Serum insulin-like growth factor-I concentration in cats with diabetes mellitus and acromegaly, J Vet Intern Med 21:892, 2007.)

performed 4 to 6 months later will usually demonstrate an increase in serum IGF-I if acromegaly is present. The increase in serum IGF-I typically coincides with development and growth of the pituitary somatotropic adenoma. Increased serum IGF-I concentrations have been identified in a small number of poorly controlled diabetic cats in which the poor control was not caused by acromegaly. Interpretation of serum IGF-I test results should always take into consideration the status of control of the diabetic state, the presence and severity of insulin resistance, and the index of suspicion for acromegaly based on review of the history, physical examination, and results of routine blood and urine tests and diagnostic imaging. Identifying an increased serum IGF-I concentration in a poorly controlled diabetic cat with insulin resistance and clinical features suggestive of acromegaly supports the diagnosis and provides justification for CT or MR imaging of the pituitary gland. Documenting a pituitary mass by CT or MR scanning (see Fig. 49-7) adds further evidence for the diagnosis and is indicated whenever the client is considering radiation treatment. It is usually necessary to administer a positive contrast agent to visualize a pituitary mass using CT or MR imaging.

A definitive diagnosis of acromegaly requires documentation of an increased baseline serum GH concentration. Baseline serum GH concentration in cats with acromegaly typically exceeds 10 ng/ml (normal concentration is less than 5 ng/ml). Unfortunately, a commercial GH assay is not available for cats.

# ACROMEGALY VERSUS HYPERADRENOCORTICISM

Hyperadrenocorticism and acromegaly are uncommon disorders that occur in older cats, have a strong association with diabetes mellitus, can cause severe insulin resistance, and are often caused by a functional pituitary macrotumor. Clinical signs related to poorly controlled diabetes mellitus are common in cats with hyperadrenocorticism and acromegaly. Additional clinical signs differ dramatically between these two disorders. Hyperadrenocorticism is a debilitating disease that results in progressive weight loss leading to cachexia and dermal and epidermal atrophy leading to extremely fragile, thin, easily torn and ulcerated skin (i.e., feline fragile skin syndrome). In contrast, conformational changes caused by the anabolic actions of chronic IGF-I secretion dominate the clinical picture in acromegaly, most notably an increase in body size, prognathia inferior, and weight gain despite poorly regulated diabetes mellitus. Feline fragile skin syndrome does not occur with acromegaly. With both disorders most of the abnormalities identified on routine blood and urine tests are caused by concurrent poorly controlled diabetes mellitus. Abdominal ultrasound may also reveal mild bilateral adrenomegaly with both disorders. Ultimately, the differentiation between the two diseases is based on results of tests of the pituitaryadrenocortical axis (see Chapter 53) and serum GH and/or IGF-1 concentrations.

# **Treatment**

Radiotherapy is currently considered the most viable treatment option for acromegaly in cats. Cobalt teletherapy involves the administration of a total dose of 45 to 48 Gy in daily fractions five days per week for 3 to 4 weeks. The clinical response to cobalt teletherapy is unpredictable and ranges from no response to a dramatic response, characterized by shrinkage of the tumor; elimination of hypersomatotropism; resolution of insulin resistance; and, in some cats, reversion to a subclinical diabetic state (see Fig. 49-7). Typically, tumor size and plasma GH and serum IGF-I concentrations decrease and insulin responsiveness improves after cobalt teletherapy, although this improvement may take 6 months or longer to occur after radiation treatment. In most treated cats that respond to radiation therapy, diabetes mellitus and/or insulin resistance recurs 6 months or longer after treatment, although growth of the pituitary mass is often not evident on CT or MR imaging.

Microsurgical transsphenoidal hypophysectomy has been shown to be effective for the treatment of feline pituitary-dependent hyperadrenocorticism, but use of this specialized surgical technique for the treatment of acromegaly has not been reported. Successful use of transsphenoidal cryotherapy of a pituitary tumor has been described in a cat with acromegaly. An effective medical treatment for acromegaly in cats has not been identified.

### **Prognosis**

The short- and long-term prognosis for cats with tumorinduced acromegaly is guarded to good and poor, respectively. The survival time has ranged from 4 to 60 months (typically 1.5 to 3 years) from the time the diagnosis of acromegaly is established. The GH-secreting pituitary tumor usually grows slowly, and neurologic signs associated with an expanding tumor are uncommon until late in the disorder. Diabetes mellitus is difficult to control, even with the administration of large doses of insulin (20 U or more/injection) given twice daily. Administration of large doses of insulin is not recommended. The severity of insulin resistance fluctuates unpredictably in cats with acromegaly, and severe, life-threatening hypoglycemia may suddenly develop after months of insulin resistance and blood glucose concentrations in excess of 400 mg/dl. To prevent severe hypoglycemia, insulin doses should not exceed 12 to 15 units per injection. Most cats with acromegaly eventually die or are euthanized because of the development of severe congestive heart failure, renal failure, respiratory distress, the neurologic signs of an expanding pituitary tumor, or coma caused by severe hypoglycemia.

# PITUITARY DWARFISM

## Etiology

Pituitary dwarfism results from a congenital deficiency of GH. Studies in German Shepherd Dog dwarfs suggest that congenital GH deficiency is caused by primary failure of differentiation of the craniopharyngeal ectoderm into normal tropic hormone-secreting pituitary cells. Pituitary cysts are commonly identified with diagnostic imaging of the pituitary region using CT or MR imaging and may enlarge as the pituitary dwarf ages. However, current belief is that pituitary cysts develop secondary to primary failure of anterior pituitary formation in most pituitary dwarfs. Pituitary dwarfism is encountered most often as a simple, autosomal recessive inherited abnormality in the German Shepherd Dog. A similar mode of inheritance has been reported in Carnelian Bear dogs. Inherited pituitary dwarfism may be due to isolated GH deficiency or may be part of a combined pituitary hormone deficiency. Concurrent deficiency in thyroid-stimulating hormone (TSH) and prolactin are most commonly identified in affected German Shepherd Dogs; ACTH secretion is preserved. Kooistra et al. (2000) hypothesize that the disorder is caused by a mutation in a developmental transcription factor that precludes effective expansion of a pituitary stem cell after differentiation of the corticotropic cells that produce ACTH. Pituitary dwarfism resulting from a mutant GH or an insensitivity to GH owing to a lack of or defect in GH receptors (e.g., Laron-type dwarfism in human beings) has not been documented in dogs or cats.

#### **Clinical Features**

#### **SIGNALMENT**

Pituitary dwarfism occurs primarily in German Shepherd Dogs, although pituitary dwarfism in other dog breeds, including the Weimaraner, Spitz, Miniature Pinscher, Carnelian Bear dog, and Labrador Retriever, and in cats has also been observed. There does not appear to be a sex-related predilection.

#### **CLINICAL SIGNS**

The most common clinical manifestations of pituitary dwarfism are lack of growth (i.e., short stature), endocrine alopecia, and hyperpigmentation of the skin (Box 49-4). Affected animals are usually normal in size during the first 2 to 4 months of life but after that grow more slowly than their litter mates. By 5 to 6 months of age, affected dogs and cats are obviously runts of the litter and do not attain full adult dimensions. Dwarfs with an isolated GH deficiency typically maintain a normal body contour and body proportions as they age (i.e., proportionate dwarfism), whereas dwarfs with combined deficiencies (most notably TSH) may acquire a square or chunky contour typically associated with congenital hypothyroidism (i.e., disproportionate dwarfism; Fig. 49-10).

The most notable dermatologic sign is retention of the lanugo or secondary hairs, with concurrent lack of the primary or guard hairs. As a result, the haircoat in a dwarf is initially soft and wooly. The lanugo hairs are easily epilated, and a bilateral symmetric alopecia gradually develops. Initially, hair loss is confined to areas of wear, such as the neck (collar) and posterolateral aspects of the thighs (from sitting). Eventually, the entire trunk, neck, and proximal limbs become alopecic, with primary hairs remaining only on the face and distal extremities. The skin is initially normal



BOX 49-4

Clinical Signs Associated with Pituitary Dwarfism

#### Musculoskeletal

Stunted growth\*
Thin skeleton, immature facial features\*
Square, chunky contour (adult)\*
Bone deformities
Delayed closure of growth plates
Delayed dental eruption

#### Reproduction

Testicular atrophy Flaccid penile sheath Failure to have estrous cycles

#### Other Signs

Mental dullness
Shrill, puppylike bark\*
Signs of secondary hypothyroidism
Signs of secondary adrenal insufficiency (uncommon)

#### **Dermatologic**

Soft, wooly haircoat\*
Retention of lanugo hairs\*
Lack of guard hairs\*
Alopecia\*
Bilaterally symmetric
Trunk, neck, proximal extremities
Hyperpigmentation of the skin\*
Thin, fragile skin
Wrinkles
Scales
Comedones
Papules
Pyoderma

Seborrhea sicca

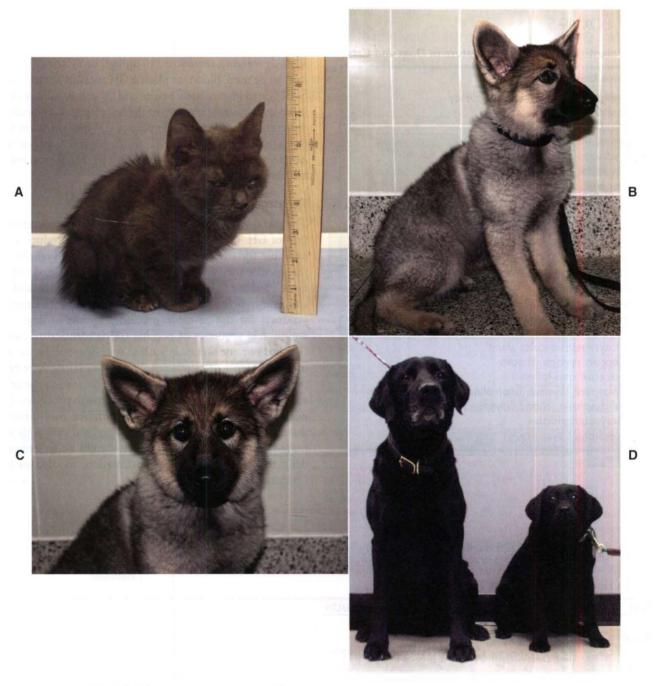
but becomes hyperpigmented, thin, wrinkled, and scaly. Comedones, papules, and secondary pyoderma frequently develop in the adult dwarf. Secondary bacterial infections are common long-term complications.

Hypogonadism may also develop, although normal reproductive function has been observed in some animals with pituitary dwarfism. In the male animal cryptorchidism, testicular atrophy, azoospermia, and a flaccid penile sheath are typical; in the female persistent anestrus is common with impaired secretion of pituitary gonadotropins.

## Clinical Pathology

Results of a CBC, serum biochemical panel, and urinalysis are usually normal in animals with uncomplicated pituitary dwarfism and isolated GH deficiency. Concurrent deficiency of TSH may result in clinicopathologic abnormalities affiliated with hypothyroidism, such as hypercholesterolemia and anemia (see Chapter 51). Deficiency of GH, IGF-I, and TSH may also affect kidney development and function, resulting in azotemia.

<sup>\*</sup>Common finding.



#### FIG 49-10

**A,** A 9-month-old male domestic short-haired cat with pituitary dwarfism. The size of the pituitary dwarf cat was similar to that of an 8-week-old kitten. Note the normal body contour and juvenile appearance. **B** and **C,** A 7-month-old female German Shepherd Dog with pituitary dwarfism. Note the normal body contour, puppy haircoat, and juvenile appearance. **D,** A 2-year-old female spayed Labrador Retriever with pituitary dwarfism sitting next to an age-matched normal Labrador Retriever to illustrate the small stature and juvenile appearance of the pituitary dwarf. All of the pituitary dwarfs presented with the primary owner complaint of failure of their pet to grow.

# **Diagnosis**

The signalment, history, and physical examination usually provide sufficient evidence for pituitary dwarfism to be included among the tentative diagnoses of short stature. Strong presumptive evidence can be obtained by ruling out other potential causes of small size (Box 49-5) after a thor-

ough evaluation of the history and physical examination findings, results of routine laboratory studies (i.e., CBC, fecal examinations, serum biochemical panel, urinalysis), and radiographic studies (Fig. 49-11). Serum IGF-I concentrations are decreased in pituitary dwarfs. Because baseline plasma GH concentrations may be low in healthy dogs and



Some Potential Causes of Small Stature in Dogs and Cats

#### **Endocrine Causes**

Congenital growth hormone deficiency Congenital hypothyroidism Juvenile diabetes mellitus Congenital hypoadrenocorticism Hyperadrenocorticism Congenital (rare) latrogenic

#### **Nonendocrine Causes**

Malnutrition

Gastrointestinal tract disorders

Megaesophagus
Inflammatory diseases
Infectious diseases
Heavy intestinal parasitism
Exocrine pancreatic insufficiency
Hepatic disorders
Portosystemic vascular shunt
Glycogen storage disease

Renal disease and failure Cardiovascular disease, anomalies Skeletal dysplasia; chondrodystrophy

Mucopolysaccharidoses

Hydrocephalus

cats, a definitive diagnosis of hyposomatotropism requires evaluation of plasma GH concentrations during a stimulation test (Table 49-7). GH-releasing hormone (GHRH, 1  $\mu$ g/kg body weight), clonidine (10  $\mu$ g/kg), or xylazine (100  $\mu$ g/kg) can be used. Blood for plasma GH measurements should be obtained immediately before and 20 and 30 minutes after intravenous administration of the secretagogue. In pituitary dwarfs there is no increase in plasma GH concentration after the administration of a GH secretagogue. A partial GH deficiency should be suspected whenever subnormal results are obtained.

#### **Treatment**

The therapy for pituitary dwarfism relies on the administration of GH. Unfortunately, an effective GH product is not available for use in dogs. Canine GH is not available for therapeutic use, GH antibody formation and legal restrictions preclude the use of biosynthetic human GH, and the concentration of biosynthetic bovine GH in commercial products for use in cattle precludes its use in dogs. The amino acid sequence of porcine GH is identical to canine GH, but porcine GH is difficult to find. If available, the recommended subcutaneous dose is 0.1 to 0.3 IU/kg three times per week for 4 to 6 weeks. Because of the synergistic influence of GH and thyroid hormone on growth processes, subnormal concentrations of thyroid hormone may diminish the effectiveness of GH therapy. Dogs and cats with suspected concurrent TSH deficiency should be treated with daily thyroid hormone supplementation, as discussed in Chapter 51.



TABLE 49-7

# Growth Hormone-Stimulation Testing Protocols

TEŞT	DESCRIPTION AND RESULTS	
Xylazine stimulation test*		
Protocol	100 µg/kg IV; plasma samples obtained before and 20 and 30 minutes after administration of xylazine	
Normal results	Twofold to fourfold increase in plasma GH 20 to 30 minutes after xylazine administration; poststimulation plasma GH > 10 ng/ml	
Adverse reactions	Sedation (common), bradycardia, hypotension, collapse, shock, seizures	
Clonidine-stimulation test		
Protocol	10 μg/kg, IV; plasma samples obtained before and 20 and 30 minutes after administration of clonidine	
Normal results	Twofold to fourfold increase in plasma GH 20 to 30 minutes after clonidine administral poststimulation plasma GH > 10 ng/ml	
Adverse reactions	Sedation (common), bradycardia, hypotension, collapse, aggressive behavior	
GHRH-stimulation test	. , , , , , , , , , , , , , , , , , , ,	
Protocol	1 μg/kg human GHRH, IV; plasma samples before and 20 and 30 minutes after GHRH	
Normal results	2 to 4 fold increase in plasma GH 20 to 30 minutes after GHRH administration; post- stimulation plasma GH > 10 ng/ml	
Adverse reactions	None reported	

<sup>\*</sup>Currently preferred GH-stimulation test.

IV, Intravenous; GH, growth hormone; GHRH, growth hormone-releasing hormone.

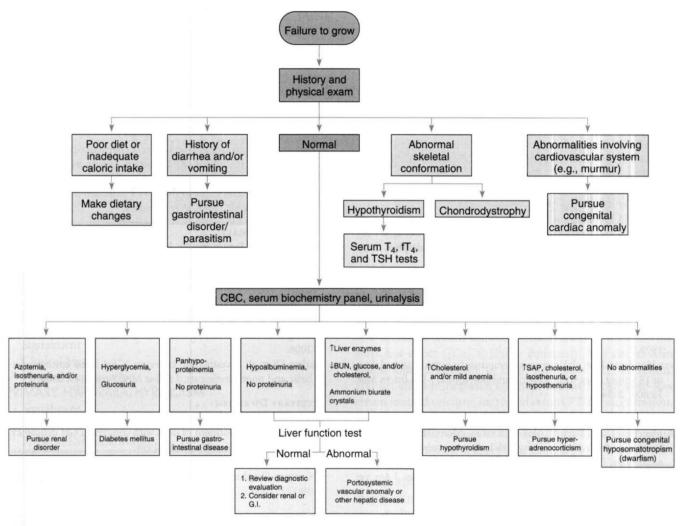


FIG 49-11
Diagnostic approach to the puppy or kitten that fails to grow. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders)

Hypersensitivity reactions (including angioedema), carbohydrate intolerance, and overt diabetes mellitus are the primary adverse reactions associated with GH injections. Frequent monitoring of urine for glycosuria and blood for hyperglycemia should be done, and GH therapy should be stopped if either develops. Regrowth of hair, thickening of the skin, and changes in serum IGF-I and glucose concentrations are used to monitor therapy. A beneficial response in the skin and haircoat usually occurs within 6 to 8 weeks of the start of GH and thyroid hormone supplementation. The hair that grows back is lanugo or secondary hairs; the growth of primary or guard hairs is variable and may occur sporadically over the body. An increase in height is dependent on the status of the growth plates at the time treatment is initiated. A significant increase in height may occur if the growth plates are open, and minimal to no change in height will occur if the growth plates have closed or are about to close at the time treatment is initiated.

An increase in body size and regrowth of a complete haircoat has been reported in pituitary dwarfs treated with medroxyprogesterone acetate at doses of 2.5 to 5.0 mg/kg body weight, initially at 3-week intervals and subsequently at 6-week intervals. Progestogens induce the expression of the GH gene in the mammary gland of dogs, resulting in GH secretion from foci of hyperplastic ductular epithelial cells and increased plasma concentrations of GH and IGF-I. Adverse reactions with progestogen treatment include recurrent pruritic pyoderma, abnormal skeletal development, mammary tumors, diabetes mellitus, acromegaly, and cystic endometrial hyperplasia. Female dogs should be ovariohysterectomized before progestogen treatment. Serum IGF-I and glucose concentrations should be monitored.

#### **Prognosis**

The long-term prognosis for animals with pituitary dwarfism is poor. Most animals die by 5 years of age despite therapy.

Death is usually a result of infections, degenerative diseases, neurologic dysfunction, or renal failure.

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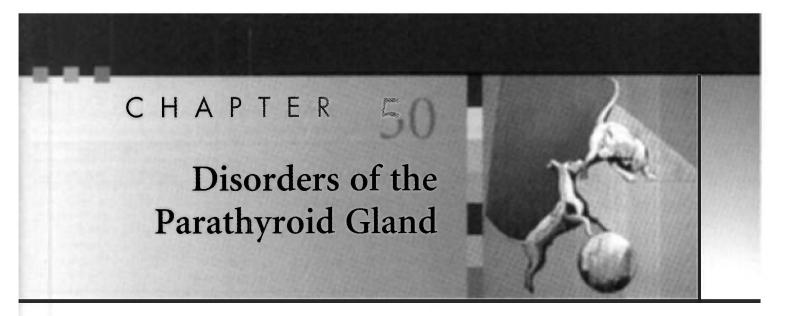
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# CHAPTER OUTLINE

CLASSIFICATION OF HYPERPARATHYROIDISM PRIMARY HYPERPARATHYROIDISM

Signalment Clinical Signs Physical Examination PRIMARY HYPOPARATHYROIDISM

Signalment Clinical Signs Physical Examination

# CLASSIFICATION OF HYPERPARATHYROIDISM

Hyperparathyroidism is a sustained increase in parathyroid hormone (PTH) secretion. Chief cells located within the parathyroid gland synthesize and secrete PTH—a peptide hormone that controls the minute-to-minute concentration of ionized calcium in the blood and extracellular fluid (ECF). The major regulator of PTH secretion is the concentration of ionized calcium in the blood. Decreased serum ionized calcium increases PTH secretion, and vice versa. PTH stimulates calcium reabsorption and inhibits phosphate reabsorption by the kidney, stimulates synthesis of the active form of vitamin D in the kidney, and stimulates bone resorption. The net effect is to increase serum ionized and total calcium concentration and decrease serum phosphorus concentration.

Hyperparathyroidism can result from a normal physiologic response to decreased serum ionized calcium concentrations (renal, nutritional, and adrenal secondary hyperparathyroidism) or a pathologic condition resulting from excessive synthesis and secretion of PTH by abnormal, autonomously functioning parathyroid chief cells (i.e., primary hyperparathyroidism [PHP]). In PHP increased secretion of PTH is maintained regardless of the serum ionized calcium concentration.

Hypercalcemia and hypophosphatemia develop as a result of the physiologic actions of PTH. In renal secondary hyperparathyroidism renal failure causes retention of phosphate and development of hyperphosphatemia. Hyperphosphatemia decreases serum ionized calcium concentration by the mass law effect ( $[Ca] \times [Pi] = constant$ ). The decrease in serum ionized calcium, in turn, stimulates PTH secretion. The net effect is increased serum phosphate, normal-to-low serum ionized calcium, increased serum PTH concentration, and diffuse parathyroid gland hyperplasia. The etiogenesis of hyperparathyroidism is similar in nutritional secondary hyperparathyroidism, except the decrease in calcium results from feeding diets containing low calcium-to-phosphorus ratios, such as beef heart or liver. Dietary calcium deficiency or phosphorus excess decreases serum calcium concentration, inducing increased PTH secretion and parathyroid gland hyperplasia. An increase in serum PTH has been documented in dogs with hyperadrenocoricism and is believed to be a compensatory response to increased calcium loss and/or increased serum phosphate concentrations—hence the term adrenal secondary hyperparathyroidism. Serum phosphate and PTH decrease and serum calcium increases after successful treatment of hyperadrenocorticism.

# PRIMARY HYPERPARATHYROIDISM

# Etiology

PHP is a disorder resulting from the excessive, relatively uncontrolled secretion of PTH by one or more abnormal parathyroid glands. The physiologic actions of PTH ultimately cause hypercalcemia and hypophosphatemia (Table 50-1). It is an uncommon disorder in the dog and rare in the cat. Parathyroid adenoma is the most common histologic finding; parathyroid carcinoma and parathyroid hyperplasia have also been described in dogs and cats but are uncommon. Parathyroid adenomas are typically small, well-encapsulated, light brown to red tumors located in close apposition to the thyroid gland (Fig. 50-1). The remaining parathyroid glands are normal, atrophied, or not visible at surgery. Parathyroid carcinomas grossly appear similar to adenomas; the

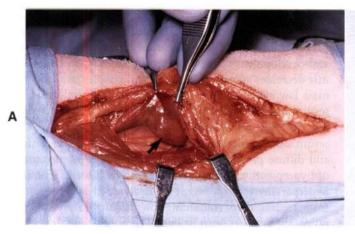


# **TABLE 50-1**

# Biologic Actions of the Hormones that Affect Calcium and Phosphorus Metabolism

		A		NET EFFECT	
HORMONE	BONE	KIDNEY	INTESTINE	SERUM CA	SERUM PO
Parathyroid hormone	Increased bone resorption	Ca absorption  ↑ PO₄ excretion	No direct effect	<b>↑</b>	<b>\</b>
Calcitonin	Decreased bone resorption	↓ Ca resorption ↓ PO <sub>4</sub> resorption	No direct effect	<b>\</b>	1
Vitamin D	Maintain Ca transport system	↓ Ca resorption	↑ Ca absorption ↑ PO₄ absorption	<b>↑</b>	1

<sup>¶,</sup> Increased; ↓, decreased. Ca, calcium; PO₄, phosphorus.



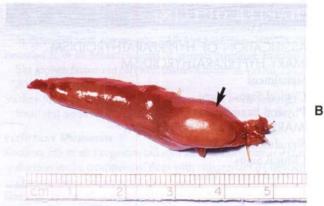


FIG 50-1

**A,** Surgical site in a 12-year-old dog with primary hyperparathyroidism (PHP). A parathyroid adenoma (arrow) can be seen in the thyroid lobe. **B,** Gross appearance of parathyroid adenoma (arrow) and thyroid lobe after removal from the dog in **A**.

diagnosis of carcinoma is based on finding certain histologic features such as capsular or vascular invasion by the tumor. The biologic behavior of parathyroid carcinoma is not well characterized in dogs and cats. Similarly, the histologic criteria for differentiating between adenoma and hyperplasia is not well established. Although involvement of multiple parathyroid glands suggests hyperplasia, adenoma involving two glands and hyperplasia involving only one gland have been identified in dogs with PHP. In addition, hyperplasia caused by renal and nutritional secondary hyperparathyroidism may not cause uniform enlargement of the parathyroid glands even though the stimulus for enlargement is the same for each gland. Differentiating hyperplasia from adenoma has important prognostic implications. The surgical removal of parathyroid adenoma(s) results in a cure, assuming at least one normal parathyroid gland remains to prevent hypoparathyroidism. In contrast, hypercalcemia caused by parathyroid hyperplasia may persist or recur weeks to months after surgery if the remaining grossly normal-appearing parathyroid tissue is hyperplastic at the time of surgery or becomes hyperplastic in the future.

#### **Clinical Features**

# **SIGNALMENT**

The age at which clinical signs of PHP appear in dogs ranges from 4 to 16 years, with a mean age of 10 years. There is no sex-related predilection. Any breed of dog can be affected, although PHP is most commonly diagnosed in the Keeshond and is an autosomal dominant, genetically transmitted disease in this breed. The age at the time of diagnosis of PHP in cats has ranged from 8 to 20 years, with a mean age of 13 years. The majority of cats have been mixed breed and Siamese. There is no apparent sex predisposition.

#### **CLINICAL SIGNS**

Clinical signs of PHP result from the physiologic actions of excessive PTH secretion rather than from the space-occupying nature of the tumor. Clinical signs are caused by hypercalcemia, which is the hallmark of this disorder, and by the presence of cystic calculi and lower urinary tract infections, which are consequences of the hypercalcemia. Clinical signs are absent in most dogs and cats with the mildest form of



BOX 50-1

Clinical Signs Associated with Primary Hyperparathyroidism in Dogs

Polyuria and polydipsia\*
Muscle weakness\*
Decreased activity\*
Lower urinary tract signs\*
Pollakiuria
Hematuria
Stranguria
Decreased appetite
Urinary incontinence
Weight loss/muscle wasting
Vomiting
Shivering/trembling

PHP, and hypercalcemia is discovered only after a serum biochemistry panel is performed, often for unrelated reasons. When clinical signs do develop, they initially tend to be nonspecific and insidious in onset. The clinical signs in dogs are typically renal, gastrointestinal, and neuromuscular in origin (Box 50-1). The most common clinical signs in cats with PHP are lethargy, anorexia, and vomiting. Less common clinical signs in cats include constipation, polyuria, polydipsia, and weight loss.

# PHYSICAL EXAMINATION

The physical examination is usually normal, which is an important diagnostic finding when differentiating dogs with PHP from dogs with hypercalcemia of malignancy (see Chapter 55). Lethargy, generalized muscle atrophy, weakness, and cystic calculi (calcium phosphate, calcium oxalate, or both types) may be noted in some dogs with PHP. The severity of weakness is variable but usually subtle. Cervical palpation of a parathyroid mass is rare in dogs with PHP. If a mass is palpated in the neck of a dog with hypercalcemia, thyroid gland carcinoma; squamous cell carcinoma; lymphoma; and, least likely, parathyroid gland carcinoma should be considered. In contrast, cats with PHP often have a palpable parathyroid mass that is typically located in the region of the thyroid gland. As such, a palpable mass in the ventral cervical region of the neck should raise suspicion for hyperthyroidism (common) as well as PHP (rare) in cats.

# Diagnosis

PHP should be suspected in a dog or cat with persistent hypercalcemia and normophosphatemia to hypophosphatemia. The serum calcium concentration is typically 12 to 15 mg/dl but can exceed 16 mg/dl. The serum ionized calcium concentration is typically 1.4 to 1.8 mmol/L but can exceed 2.0 mmol/L. The serum phosphorus concentration is typically less than 4 mg/dl, unless concurrent renal insufficiency is present. Although hypercalcemia in dogs and

cats has several causes (Table 50-2), the primary differential diagnoses for hypercalcemia and hypophosphatemia are humoral hypercalcemia of malignancy (most notably lymphoma in dogs and carcinomas in cats) and PHP (see Chapter 55). The history, findings on physical examination, results of routine blood and urine tests, thoracic radiographs, abdominal and cervical ultrasound, and measurement of PTH and parathyroid hormone-related peptide (PTHrp) will usually establish the diagnosis. With PHP clinical signs are usually mild to absent, the physical examination is normal, and results of routine blood work, thoracic and abdominal radiography, and abdominal ultrasonography are unremarkable, except for hypercalcemia, hypophosphatemia, and cystic calculi. Additional tests used to identify lymphoma as the cause of hypercalcemia (i.e., cytologic evaluations of bone marrow and lymph node, liver, and splenic aspirates and PTHrp concentrations) are normal in dogs with PHP.

Renal failure in a dog with hypercalcemia can create a diagnostic dilemma. Fortunately, development of hypercalcemia-induced renal failure rarely occurs in dogs with PHP. Prolonged severe hypercalcemia may cause progressive nephrocalcinosis, renal damage, and azotemia, but most dogs with PHP have mild hypercalcemia and concurrent hypophosphatemia; the latter protects the kidney by keeping the calcium × phosphorus product less than 50. Measurement of serum ionized calcium concentration will help identify the etiology of hypercalcemia in dogs with concurrent renal failure. Serum ionized calcium concentration is typically normal in dogs with renal failure-induced hypercalcemia and increased in dogs with PHP and concurrent renal failure. Urine specific gravity is usually not helpful when assessing renal function in dogs with hypercalcemia because of the interference of calcium with the actions of vasopressin on renal tubular cells. Urine specific gravities less than 1.015 are common in dogs with PHP. Hematuria, pyuria, bacteriuria, and crystalluria may be identified if cystic calculi and secondary bacterial cystitis develop. Hypercalciuria, proximal renal tubular acidosis with impaired bicarbonate resorption, and the production of alkaline urine may predispose dogs to the development of cystic or renal calculi and bacterial cystitis. In one study urinary tract infection was identified in 29% and cystic calculi in 31% of 210 dogs with PHP (Feldman et al., 2005). Uroliths are typically composed of calcium phosphate, calcium oxalate, or mixtures of the two salts.

Cervical ultrasound should identify one or more enlarged parathyroid glands in dogs and cats with PHP (Fig. 50-2). The parathyroid glands of healthy dogs are typically 3 mm or less in maximum width when visualized ultrasonographically. The maximum width of the abnormal parathyroid glands ranged from 3 to 23 mm (median 6 mm) in 130 dogs with PHP (Feldman et al., 2005). A solitary parathyroid mass was identified in 89%, and two parathyroid masses were identified in 10% of the dogs.

Measurement of baseline serum PTH concentration is used to establish the diagnosis of PHP. The two-site immunoradiometric (IRMA) assay system is currently used by

<sup>\*</sup>Common sign.



# Causes of Hypercalcemia in Dogs and Cats

#### DISORDER

Primary hyperparathyroidism Hypercalcemia of malignancy

Humorally mediated: LSA, apocrine gland adenocarcinoma, carcinoma (nasal, mammary gland, gastric, thyroid, pancreatic, pulmonary)

Locally osteolytic (multiple myeloma, LSA, squamous cell carcinoma, osteosarcoma, fibrosarcoma)

Hypervitaminosis D

Cholecalciferol rodenticides, plants

Excessive supplementation

Hypoadrenocorticism

Renal failure

Idiopathic—cats

Granulomatous disease (uncommon)

Systemic mycosis—Blastomycosis

Schistosomiasis, FIP

Nonmalignant skeletal disorder (rare)

Osteomylelitis

Hypertrophic osteodystrophy

latrogenic disorder

Excessive calcium supplementation

Excessive oral phosphate binders

Dehydration (mild hyercalcemia)

Factitious disorder

Lipemia

Postprandial measurement

Young animal (<6 months)

Laboratory error

#### TESTS TO HELP ESTABLISH THE DIAGNOSIS

Serum PTH concentration, cervical ultrasound, surgery Physical examination, thoracic and abdominal radiography, abdominal ultrasonography, aspiration of lymph nodes, liver, spleen and bone marrow, serum PTHrp

History, serum biochemistry panel, serum vitamin D concentration

Serum electrolytes, ACTH stimulation test Serum biochemistry panel, urinalysis Rule out by exclusion

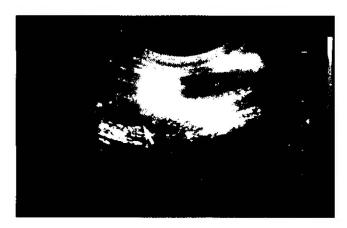
Thoracic radiography, abdominal ultrasonography, fundic examination, cytologic studies of pulmonary wash samples or intestinal biopsy specimens, serum fungal titers

Radiography of peripheral skeleton

History

Repeat calcium measurement

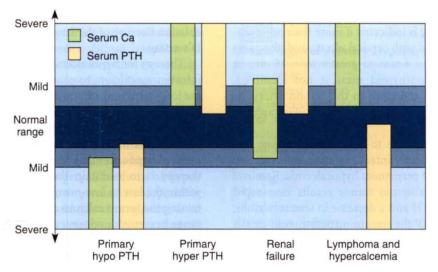
PTH, Parathyroid hormone; LSA, lymphosarcoma; PTHrp, parathyroid hormone-related peptide; ACTH, adrenocorticotropic hormone; FIP, feline infectious peritonitis.



#### FIG 50-2

Ultrasound image of the right thyroid lobe of a 13-year-old Labrador Retriever with hypercalcemia and primary hyperparathyroidism. A hypoechoic mass is seen in the region of the parathyroid gland (arrow). Hypercalcemia resolved following heat ablation of the parathyroid mass.

most veterinary laboratories and is considered the most reliable assay system for PTH quantification in dogs and cats. Most laboratories have a similar PTH reference range for dogs (2 to 13 pmol/L) and cats (0.8 to 4.6 pmol/L). The major regulator of PTH secretion is the concentration of ionized calcium in the blood. Decreased serum ionized calcium increases PTH secretion, and vice versa. Serum PTH test results should always be interpreted in conjunction with serum calcium or, preferably, serum ionized calcium measured from the same blood sample. If the parathyroid gland is functioning normally, the serum PTH concentration should be below the reference range or undetectable in the face of hypercalcemia because of the inhibitory effects of an increased serum calcium concentration on parathyroid gland function. Dogs with nonparathyroid-induced hypercalcemia should also have low to undetectable serum PTH concentrations. Serum PTH concentration within or above the reference range is inappropriate in the face of hypercalcemia and indicative of an autonomously functioning



**FIG 50-3**Ranges of the serum calcium and parathyroid hormone concentrations in the more common disorders causing alterations in serum calcium concentration, parathyroid gland function, or both. *PTH*, Parathyroid hormone; *hypo PTH*, hypoparathyroidism; *hyper PTH*, hyperparathyroidism.

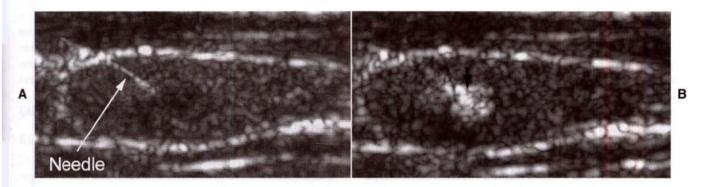


FIG 50-4

**A,** Ultrasound image of the left thyroid lobe of an 12-year-old Keeshond with hypercalcemia. A mass is in the region of the parathyroid gland (arrow), and a needle has been inserted into the mass using ultrasound guidance before heat ablation of the mass. **B,** Heat is being administered to the mass, causing hyperechogenicity of the mass (arrow).

parathyroid gland (Fig. 50-3). In 185 dogs with PHP none had serum PTH concentration below the reference range, 45% were in the lower half of the reference range (2.3 to 7.9 pmol/L), 28% were in the upper half of the reference range (8.0 to 13.0 pmol/L), and 27% had increased serum PTH concentrations (13 to 121 pmol/L; Feldman et al., 2005).

#### **Treatment**

Surgical removal of the abnormal parathyroid tissue is the treatment of choice. Slatter (2003) and Fossum (2007) have adequately described the surgical techniques for the thyroparathyroid complex (see Suggested Readings). Almost all dogs and cats with PHP have a solitary, easily identified parathyroid adenoma (see Fig. 50-1). Enlargement of more than one parathyroid gland indicates the presence of either multiple adenomas or parathyroid hyperplasia. If none of

the parathyroid glands appear enlarged or if all appear small, the diagnosis of PHP must be questioned and hypercalcemia stemming from occult neoplasia or PTH production by a parathyroid tumor in an ectopic site (e.g., cranial mediastinum) or by a nonparathyroid tumor should be considered.

Chemical (i.e., ethanol) and heat ablation of abnormal parathyroid tissue performed under ultrasound guidance are also effective treatments for PHP (Fig. 50-4). Surgery is avoided, anesthetic time is significantly reduced, and there are no incisions or issues related to wound healing. However, the management of the dog after chemical or heat ablation is identical to the management after surgical removal of the parathyroid mass. In a recent retrospective study surgical removal, heat ablation, and chemical ablation of the parathyroid mass were successful in controlling hypercalcemia in 94%, 90%, and 72% of dogs treated for PHP, respectively

(Rasor et al., 2007). Not all dogs are candidates for chemical or heat ablation. Surgery is indicated if more than one parathyroid mass is identified with cervical ultrasound, the parathyroid mass is less than 4 mm or greater than 15 mm in maximum width, a parathyroid mass is not identified, the parathyroid mass is too close to the carotid artery, or cystic calculi are identified with abdominal radiographs or ultrasound.

An attempt must be made to ensure that at least one parathyroid gland remains intact to maintain calcium homeostasis and prevent permanent hypocalcemia. Removal or ablation of the parathyroid tumor results in a rapid decline in circulating PTH and a decrease in serum calcium. In the early stages of PHP the remaining parathyroid glands may secrete PTH in response to the decrease in serum calcium, thereby preventing development of severe hypocalcemia. In dogs with more advanced PHP, atrophy of the normal parathyroid glands may prevent a response to the decrease in serum calcium, leading to severe hypocalcemia and clinical signs within 7 days of surgery or ablation. In these dogs intravenous and oral calcium and oral vitamin D therapy must be initiated to correct and/or prevent hypocalcemia.

There are two approaches for managing the dog (and cat) once the parathyroid tumor has been removed with surgery or ablation. One approach is to arbitrarily treat all dogs with oral calcium and vitamin D at the time the parathyroid tumor is removed, and another approach is to withhold calcium and vitamin D therapy until the serum calcium concentration decreases below a safe concentration, typically a serum calcium or ionized calcium concentration of 9.0 mg/ dl and 0.9 mmol/L, respectively, and before clinical signs of hypocalcemia develop. Regardless of which approach is taken, serum total or ionized calcium should be monitored once or twice a day until the serum calcium concentration is stable and in the reference range. I prefer to withhold calcium and vitamin D therapy in dogs in which I suspect parathyroid gland atrophy is mild and calcium and vitamin D therapy may not be needed. The higher the preoperative serum calcium concentration or the more chronic the hypercalcemic condition, or both, the more likely the dog will become clinically hypocalcemic after removal of the abnormal parathyroid gland or glands. As a general rule, I do not initially treat hyperparathyroid dogs with oral calcium and vitamin D if the serum calcium or ionized calcium concentration before surgery or ablation is less than 14 mg/dl or 1.6 mmol/L, respectively, and hypercalcemia has been present for less than 6 months. Serum calcium or ionized calcium concentrations greater than 14 mg/dl and 1.6 mmol/L, respectively, and hypercalcemia that has been present for greater than 6 months suggest the existence of significant atrophy of the remaining parathyroid glands and a high probability for the development of signs of hypocalcemia after surgery or ablation. In these dogs oral calcium and vitamin D therapy is started at the time PHP is treated. In dogs with severe hypercalcemia (total calcium or ionized calcium > 18 mg/dl and 2.0 mmol/L, respectively), vitamin D

therapy can be initiated 24 to 36 hours before surgery or ablation because of the known delay in the onset of vitamin D's action.

Therapy for hypocalcemia includes the administration of intravenous calcium to control immediate clinical signs and the long-term oral administration of calcium and vitamin D supplements to maintain low-normal blood calcium concentrations while the parathyroid gland atrophy resolves. (See Chapter 55 and Box 55-7 for details about the management of hypocalcemia.) The goal of calcium and vitamin D therapy is to maintain the serum calcium concentration within the low to low-normal range (9 to 10 mg/dl). Maintaining the serum calcium concentration in the low-normal range prevents development of clinical signs of hypocalcemia, minimizes the risk of hypercalcemia, and stimulates a return of function in the remaining atrophied parathyroid glands. Once the parathyroid glands regain control of calcium homeostasis and the serum calcium concentration is stable in the dog or cat in the home environment, the calcium and vitamin D supplements can be gradually withdrawn over a period of 3 to 6 months. This gradual withdrawal allows time for the parathyroid glands to become fully functional and thereby prevents hypocalcemia. Vitamin D therapy is withdrawn by gradually increasing the number of days between administrations. The dosing interval should be increased by 1 day every 2 to 3 weeks, after the serum calcium concentration has been measured and found to be 9 mg/dl or greater. Vitamin D therapy can be discontinued once the dog or cat is clinically normal, the serum calcium concentration is stable between 9 and 11 mg/dl, and the vitamin D dosing interval is every 7 days.

## **Prognosis**

The prognosis for dogs and cats undergoing surgical or ablation therapy for PHP is excellent, assuming severe hypocalcemia is avoided postoperatively and PHP is caused by a parathyroid adenoma. Hypercalcemia may recur weeks to months after surgery in dogs and cats with PHP caused by parathyroid hyperplasia if one or more parathyroid glands have been left in situ.

# PRIMARY HYPOPARATHYROIDISM

#### **Etiology**

Primary hypoparathyroidism develops as a result of an absolute or relative deficiency in the secretion of PTH. This deficiency ultimately causes hypocalcemia and hyperphosphatemia because of a loss of the effects of PTH on bone, kidney, and intestine (see Table 50-1). The major signs of hypoparathyroidism are directly attributable to the decreased concentration of ionized calcium in the blood, which leads to increased neuromuscular activity.

Spontaneous primary hypoparathyroidism is uncommon in dogs and cats. Most cases are classified as idiopathic (i.e., there is no evidence of trauma, malignant or surgical destruction, or other obvious damage to the neck or parathyroid glands). The glands are difficult to locate visually and show microscopic evidence of atrophy. Histologic evaluation of the parathyroid gland may reveal a diffuse lymphocytic, plasmacytic infiltration and fibrous connective tissue, suggesting an underlying immune-mediated cause of the disorder.

latrogenic hypoparathyroidism after performance of bilateral thyroidectomy for the treatment of hyperthyroidism is common in cats. The parathyroid tissue in such animals may be excised or traumatized, or its blood supply may be compromised during surgery. This form of hypoparathyroidism may be transient or permanent, depending on the viability of the parathyroid gland or glands saved at the time of surgery. Only one viable parathyroid gland is needed to maintain a normal serum calcium concentration.

Transient hypoparathyroidism may develop secondary to severe magnesium depletion (serum magnesium concentration <1.2 mg/dl). Severe magnesium depletion may suppress PTH secretion without parathyroid destruction, increase end-organ resistance to PTH, and impair the synthesis of the active form of vitamin D (i.e., calcitriol). The end result is mild hypocalcemia and hyperphosphatemia. Magnesium repletion reverses the hypoparathyroidism. Serum magnesium concentrations in dogs and cats with spontaneous primary hypoparathyroidism usually have been normal when measured. (See Chapter 55 for more information on magnesium.)

# **Clinical Features**

#### **SIGNALMENT**

The age at which the clinical signs of hypoparathyroidism appear in dogs ranges from 6 weeks to 13 years, with a mean of 4.8 years. There may be a sex-related predisposition in female dogs. There is no apparent breed-related predisposition, although Toy Poodles, Miniature Schnauzers, Labrador Retrievers, German Shepherd Dogs, and Terriers are commonly affected breeds. However, this increased prevalence may merely reflect the popularity of these breeds. Only a few cases of naturally acquired primary hypoparathyroidism in cats have been reported. To date, these cats have been young to middle-aged (6 months to 7 years), of several breeds, and usually male.

# **CLINICAL SIGNS**

The clinical signs and physical examination findings in dogs and cats with primary hypoparathyroidism are similar. The major clinical signs are directly attributable to hypocalcemia, most notably its effects on the neuromuscular system. Neuromuscular signs include nervousness, generalized seizures, focal muscle twitching, rear-limb cramping or tetany, ataxia, and weakness (Box 50-2). Additional signs include lethargy, inappetence, intense facial rubbing, and panting. The onset of clinical signs tends to be abrupt and severe and to occur more frequently during exercise, excitement, and stress. Clinical signs also tend to occur episodically. Episodes of



BOX 50-2

Clinical Signs of Primary Hypoparathyroidism in Dogs

Nervousness
Generalized seizures
Rear leg cramping or pain
Focal muscle fasciculations, twitching
Ataxia, stiff gait
Facial rubbing (intense)
Aggressive behavior
Panting
Weakness
Inappetence
Listlessness, lethargy

Biting, licking paws (intense)

clinical hypocalcemia are interspersed with relatively normal periods, lasting minutes to days. Interestingly, hypocalcemia persists during these clinically "normal" periods,

#### PHYSICAL EXAMINATION

The most common physical examination findings are related to muscular tetany and include a stiff gait; muscle rigidity; a tense, splinted abdomen; and muscle fasciculations. Fever, panting, and nervousness, often so pronounced that they interfere with the examination, are also common. Potential cardiac abnormalities include bradycardia, paroxysmal tachyarrhythmias, muffled heart sounds, and weak femoral pulses. Cataracts have been noted in a few dogs and cats with primary hypoparathyroidism. Cataracts were small, punctate-to-linear, white opacities that were randomly distributed in the anterior and posterior cortical subcapsular region of the lens; there was no loss of vision. The physical examination is occasionally normal, despite the previous history of neuromuscular disorders.

#### Diagnosis

Primary hypoparathyroidism should be suspected in a dog or cat with persistent hypocalcemia, hyperphosphatemia, and normal renal function. The serum calcium concentration is usually less than 7 mg/dl, the serum ionized calcium is usually less than 0.8 mmol/L, and the serum phosphorus is usually greater than 6 mg/dl. Low serum calcium and high serum phosphorus concentrations can also be encountered during nutritional and renal secondary hyperparathyroidism, after phosphate-containing enema, and during tumor lysis syndrome. The diagnosis of primary hypoparathyroidism is established by identifying an undetectable serum PTH concentration in the face of severe hypocalcemia in a dog or cat in which other causes of hypocalcemia have been ruled out (Table 50-3). Most causes of hypocalcemia can be identified after evaluation of the history, findings on physical examination, and results of routine blood and urine tests and an abdominal ultrasound. The history and physical examination findings are essentially unremarkable in dogs



# Causes of Hypocalcemia in Dogs and Cats

DISORDER	TESTS TO HELP ESTABLISH THE DIAGNOSIS
Primary hypoparathyroidism Idiopathic Posthyroidectomy	History, serum PTH concentration, rule out other causes
Puerperal tetany	History
Renal failure	Serum biochemistry panel, urinalysis
Acute	caram distincting partially similary sign
Chronic	
Ethylene glycol toxicity	History, urinalysis
Acute pancreatitis	Physical findings, abdominal ultrasound, serum PLI
Intestinal malabsorption syndromes	History, digestion and absorption tests, intestinal biopsy
Hypoproteinemia or hypoalbuminemia	Serum biochemistry panel
Hypomagnesemia	Serum total and ionized Mg
Nutritional secondary hyperparathyroidism	Dietary/History
Tumor lysis syndrome	History
Phosphate-containing enemas	History
Anticonvulsant medications	History
NaHCO <sub>3</sub> administration	History
Laboratory error	Repeat calcium measurement

PTH, parathyroid hormone; PLI, pancreatic lipase immunoreactivity; Mg, magnesium.

and cats with primary hypoparathyroidism, other than those findings caused by hypocalcemia. The only relevant abnormalities identified on routine blood and urine tests are severe hypocalcemia and, in most dogs and cats, hyperphosphatemia. The serum total protein, albumin, urea nitrogen, creatinine, and magnesium concentrations are normal. Abdominal ultrasound is also normal.

Measurement of serum PTH concentration helps confirm a diagnosis of primary hypoparathyroidism. Blood for PTH determination should be obtained before the initiation of calcium and vitamin D therapy while the animal is still hypocalcemic. The two-site IRMA assay system is currently used by most veterinary laboratories and is considered the most reliable assay system for PTH quantification in dogs and cats. Interpretation of the serum PTH concentration must be done in conjunction with the serum calcium concentration. If the parathyroid gland is functioning normally, the serum PTH concentration should be increased in the face of hypocalcemia because of the stimulatory effects of a decreased serum ionized calcium concentration on parathyroid gland function. A low-to-undetectable serum PTH concentration in a hypocalcemic dog or cat is strongly suggestive of primary hypoparathyroidism (see Fig. 50-3). Dogs and cats with nonparathyroid-induced hypocalcemia should have normal or high serum PTH concentrations; the exceptions are those disorders causing severe hypomagnesemia.

# **Treatment**

The therapy for primary hypoparathyroidism involves the administration of vitamin D and calcium supplements (see Chapter 55 and Box 55-7). Therapy is typically divided into

two phases. The first phase (i.e., acute therapy) should initially control hypocalcemic tetany and involves the slow administration of calcium gluconate (not calcium chloride) intravenously, to effect. Once clinical signs of hypocalcemia are controlled, calcium gluconate should then be administered by continuous intravenous infusion until orally administered calcium and vitamin D therapy (i.e., second phase of therapy) becomes effective. Calcium gluconate is initially administered at a dose of 60 to 90 mg/kg per day (approximately 2.5 ml/kg of 10% calcium gluconate added to the infusion solution and administered every 6 to 8 hours). Calcium should not be added to solutions containing lactate, bicarbonate, acetate, or phosphates because of the potential for precipitation problems. Serum calcium concentrations should be monitored twice a day and the rate of infusion adjusted as needed to control clinical signs and maintain the serum calcium concentration greater than 8 mg/dl.

The second phase of therapy (i.e., maintenance therapy) should maintain the blood calcium concentration between 8 and 10 mg/dl through the daily administration of vitamin D and calcium. These calcium concentrations are above the level at which there is a risk for clinical hypocalcemia and below the level at which hypercalciuria (risk of calculi formation) or severe hypercalcemia and hyperphosphatemia (risk of nephrocalcinosis and renal failure) may occur. Maintenance therapy should be initiated once the hypocalcemic tetany is controlled with intravenous calcium therapy. The onset of action of vitamin D varies depending on the formulation of vitamin D that is administered. In general, 1,25-dihydroxy-vitamin D<sub>3</sub> (calcitriol) has the fastest onset of

action and is preferred for treating hypoparathyroidism. The initial dosage of calcitriol is 0.02 to 0.03 µg/kg/day. Dogs and cats should ideally remain hospitalized until their serum calcium concentration remains between 8 and 10 mg/dl without parenteral support. Serum calcium concentrations should be monitored weekly, with the vitamin D dose adjusted to maintain a concentration of 8 to 10 mg/dl. The aim of therapy is to prevent hypocalcemic tetany and not induce hypercalcemia. Serum calcium concentrations of more than 10 mg/dl are unnecessary to prevent tetany and only increase the likelihood of unwanted hypercalcemia.

Once the serum calcium concentration has stabilized, attempts can be made to slowly taper the dose of oral calcium and then vitamin D to the lowest dose that maintains the serum calcium concentration between 8 and 10 mg/dl. Vitamin D is critical for establishing and maintaining a normal blood calcium concentration. Most dogs and cats with primary hypoparathyroidism require permanent vitamin D therapy. The calcium supplement can often be gradually tapered over a period of 2 to 4 months and then stopped once the animal's serum calcium concentration is stable between 8 and 10 mg/dl. Calcium in the diet is often sufficient for maintaining the calcium needs of the animal. Supplementing the diet with calcium-rich foods (e.g., dairy products) helps ensure an adequate source of dietary calcium. Once the animal's serum calcium concentration is stable and maintenance therapy has become established, reevaluation of the serum calcium concentration every 3 to 4 months is advisable.

# **Prognosis**

The prognosis depends on the dedication of the client. The prognosis is excellent if proper therapy is instituted and timely reevaluations are performed. Proper management requires close monitoring of the serum calcium concentration. The more frequent the rechecks, the better the chance

of preventing extremes in the concentration and the better the chance of a normal life expectancy.

# Suggested Readings

Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.

Fossum TW: Small animal surgery, ed 3, St Louis, 2007, Mosby. Slatter D: Textbook of small animal surgery, ed 3, Philadelphia, 2003, WB Saunders.

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Feldman EC et al: Pretreatment clinical and laboratory findings in dogs with primary hyperparathyroidism: 210 cases (1987-2004), *J Am Vet Med Assoc* 227:756, 2005.

Gear RNA et al: Primary hyperparathyroidism in 29 dogs: diagnosis, treatment, outcome and associated renal failure, *J Small Anim Pract* 46:10, 2005.

Goldstein RE et al: Inheritance, mode of inheritance, and candidate genes for primary hyperparathyroidism in Keeshonden, *J Vet Intern Med* 21:199, 2007.

Long CD et al: Percutaneous ultrasound-guided chemical parathyroid ablation for treatment of primary hyperparathyroidism in dogs, J Am Vet Med Assoc 215:217, 1999.

Pollard RE et al: Percutaneous ultrasonographically guided radiofrequency heat ablation for treatment of primary hyperparathyroidism in dogs, J Am Vet Med Assoc 218:1106, 2001.

Rasor L et al: Retrospective evaluation of three treatment methods for primary hyperparathyroidism in dogs, *J Am Anim Hosp Assoc* 43:70, 2007.

Tebb AJ et al: Canine hyperadrenocorticism: effects of trilostane on parathyroid hormone, calcium and phosphate concentration, *J Small Anim Pract* 46:537, 2005.

#### PRIMARY HYPOPARATHYROIDISM

Barber PJ: Disorders of the parathyroid glands, J Fel Med Surg 6:259, 2004.

# CHAPTER Disorders of the Thyroid Gland

# CHAPTER OUTLINE

#### HYPOTHYROIDISM IN DOGS

Dermatologic Signs

Neuromuscular Signs

Reproductive Signs

Miscellaneous Clinical Signs

Myxedema Coma

Cretinism

Autoimmune Polyendocrine Syndromes

Dermatohistopathologic Findings

Ultrasonographic Findings

Tests of Thyroid Gland Function

Factors Affecting Thyroid Gland Function Tests

Diagnosis in a Previously Treated Dog

Diagnosis in Puppies

Therapy with Sodium Levothyroxine (Synthetic T<sub>4</sub>)

Response to Sodium Levothyroxine Therapy

Failure to Respond to Sodium Levothyroxine Therapy

Therapeutic Monitoring

Thyrotoxicosis

# HYPOTHYROIDISM IN CATS HYPERTHYROIDISM IN CATS

Signalment

Clinical Signs

Physical Examination

Common Concurrent Problems

# CANINE THYROID NEOPLASIA

Surgery

Megavoltage Irradiation

Chemotherapy

Radioactive Iodine

Oral Antithyroid Drugs

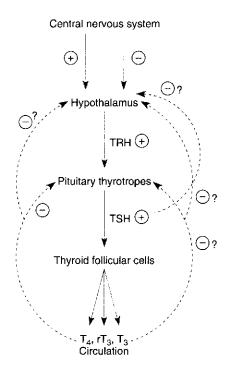
#### HYPOTHYROIDISM IN DOGS

# **Etiology**

Structural or functional abnormalities of the thyroid gland can lead to deficient production of thyroid hormones. A convenient classification scheme for hypothyroidism has been devised that is based on the location of the problem within the hypothalamic-pituitary-thyroid gland complex (Fig. 51-1). Primary hypothyroidism is the most common form of this disorder in dogs; it results from problems within the thyroid gland, usually destruction of the thyroid gland (Box 51-1). The two most common histologic findings in this disorder are lymphocytic thyroiditis and idiopathic atrophy of the thyroid gland (Fig. 51-2). Lymphocytic thyroiditis is an immune-mediated disorder characterized by a diffuse infiltration of lymphocytes, plasma cells, and macrophages into the thyroid gland. The factors that trigger the development of lymphocytic thyroiditis are poorly understood. Genetics undoubtedly plays a major role, especially given the increased incidence of this disorder in certain breeds and in certain lines within a breed (Table 51-1). Environmental risk factors have not been well defined in the dog. A link between infection-induced damage to the thyroid gland and development of lymphocytic thyroiditis has been the subject of speculation but has not been proved. Vaccine administration has also been hypothesized to be a contributing factor for development of lymphocytic thyroiditis but also has not been proved.

Destruction of the thyroid gland is progressive, and clinical signs may not become evident until more than 75% of the gland is destroyed. Development of decreased serum thyroid hormone concentrations and clinical signs is usually a gradual process, often requiring 1 to 3 years to develop, which suggests that the destructive process is slow.

Idiopathic atrophy of the thyroid gland is characterized by loss of the thyroid parenchyma. There is no inflammatory infiltrate, even in areas where small follicles or follicular remnants are present in the thyroid gland. Tests for lymphocytic thyroiditis are negative. The cause of idiopathic thyroid atrophy is not known. It may be a primary degenerative



**FIG 51-1** The hypothalamic-pituitary-thyroid gland axis. *TRH*, Thyrotropin-releasing hormone; *TSH*, thyrotropin;  $T_4$ , thyroxine;  $T_3$ , 3,5,3'-triiodothyronine;  $T_3$ , 3,3',5'-triiodothyronine; +, stimulation; -, inhibition.

disorder or represent an end stage of autoimmune lymphocytic thyroiditis.

Secondary hypothyroidism results from failure of pituitary thyrotrophs to develop (pituitary hypoplasia causing pituitary dwarfism; see Chapter 49) or from dysfunction within the pituitary thyrotropic cells causing impaired secretion of thyroid-stimulating hormone (TSH) and a "secondary" deficiency in thyroid hormone synthesis and secretion. Follicular atrophy in the thyroid gland gradually develops owing to lack of TSH. Secondary hypothyroidism could also result from destruction of pituitary thyrotrophs (e.g., pituitary neoplasia [rare]) or suppression of thyrotroph function by hormones or drugs (e.g., glucocorticoids [common]; see Box 51-1).

Tertiary hypothyroidism is a deficiency in the secretion of thyrotropin-releasing hormone (TRH) by peptidergic neurons in the supraoptic and paraventricular nuclei of the hypothalamus. Lack of TRH secretion should cause a deficiency in TSH secretion and secondary follicular atrophy in the thyroid gland. Tertiary hypothyroidism has not been reported in dogs.

Congenital primary hypothyroidism is uncommon in dogs and has been caused by deficient dietary iodine intake, dyshormonogenesis (i.e., an iodine organification defect), and thyroid dysgenesis. Secondary hypothyroidism resulting from an apparent deficiency of TSH has also been reported in a family of Giant Schnauzers and in a Boxer. Pedigree analysis showed that it may be inherited in an autosomal



#### Potential Causes of Hypothyroidism in Dogs

#### **Primary Hypothyroidism**

Lymphocytic thyroiditis Idiopathic atrophy Neoplastic destruction latrogenic Surgical removal Antithyroid medicatic

Antithyroid medications Radioactive iodine treatment Drugs (e.g., sulfamethoxazole)

#### Secondary Hypothyroidism

Pituitary malformation
Pituitary cyst
Pituitary hypoplasia
Pituitary destruction
Neoplasia
Pituitary thyrotropic cell suppression
Naturally acquired hyperadrenoo

Naturally acquired hyperadrenocorticism
Euthyroid sick syndrome
latrogenic causes

Drug therapy, most notably glucocorticoids Radiation therapy Hypophysectomy

#### Tertiary Hypothyroidism

Congenital hypothalamic malformation (?) Acquired destruction of hypothalamus (?)

#### Congenital Hypothyroidism

Thyroid gland dysgenesis (aplasia, hypoplasia, ectasia) Dyshormonogenesis: iodine organification defect Deficient dietary iodine intake

recessive fashion in the family of Giant Schnauzers. Development of an enlarged thyroid gland (i.e., goiter) depends on the etiology. If the hypothalamic-pituitary-thyroid gland axis is intact (e.g., as occurs with an iodine organification defect), goiter will develop, and if it is not intact (e.g., as occurs with pituitary TSH deficiency), goiter will not develop.

# **Clinical Features**

Clinical signs of the more common forms of primary hypothyroidism usually develop during middle age (i.e., 2 to 6 years). Clinical signs tend to develop at an earlier age in breeds at increased risk than in other breeds (see Table 51-1). There is no apparent sex-related predilection.

Clinical signs are quite variable and depend in part on the age of the dog at the time a deficiency in thyroid hormone develops (Box 51-2). Clinical signs may also differ between breeds. For example, truncal alopecia may dominate in some breeds, whereas thinning of the haircoat dominates in other breeds. In adult dogs the most consistent clinical signs of hypothyroidism result from decreased cellular metabolism

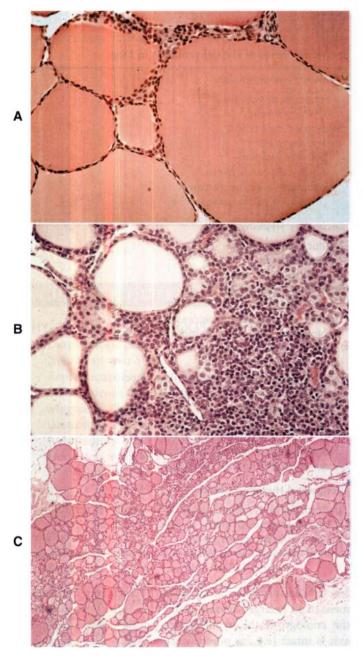


FIG 51-2

Histologic section of a thyroid gland from a healthy dog (A), from a dog with lymphocytic thyroiditis and hypothyroidism (B), and from a dog with idiopathic atrophy of the thyroid gland and hypothyroidism (C). Note the mononuclear cell infiltration, disruption of the normal architecture, and loss of colloid-containing follicles in B and the small size of the gland, decrease in follicular size and colloid content, and lack of a cellular infiltration in C, compared with A. (A and B, Hematoxylin and eosin stain; magnification ×250; C, hematoxylin and eosin stain; magnification ×40). (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)



# TABLE 51-1

Dog Breeds Reported to Have an Increased Prevalence of Thyroid Hormone Autoantibodies

BREED	ODDS RATIO*
Deliator	2.41
Pointer	3.61
English Setter	3.44
English Pointer	3.31
Skye Terrier	3.04
German Wirehaired Pointer	2.72
Old English Sheepdog	2.65
Boxer	2.37
Maltese	2.25
Kuvasz	2.18
Petit Basset Griffon Vendeen	2.16
American Staffordshire Terrier	1.84
Beagle	1.79
American Pit Bull Terrier	1.78
Dalmatian	1.74
Giant Schnauzer	1.72
Rhodesian Ridgeback	1.72
Golden Retriever	1.70
Shetland Sheepdog	1.69
Chesapeake Bay Retriever	1.56
Siberian Husky	1.45
Brittany Spaniel	1.42
Borzoi	1.39
Australian Shepherd	1.28
Doberman Pinscher	1.24
Malamute	1.22
Cocker Spaniel	1.17
Mixed	1.05

From Nachreiner RF et al: Prevalence of serum thyroid hormone autoantibodies in dogs with clinical signs of hypothyroidism, J Am Vet Med Assoc 220:466, 2002.

and its effects on the dog's mental status and activity. Most dogs with hypothyroidism show some mental dullness, lethargy, exercise intolerance or unwillingness to exercise, and a propensity to gain weight without a corresponding increase in appetite or food intake. These signs are often gradual in onset, subtle, and not recognized by the client until after thyroid hormone supplementation has been initiated. Additional clinical signs of hypothyroidism typically involve the skin and, less commonly, the neuromuscular system.

#### **DERMATOLOGIC SIGNS**

Alterations in the skin and haircoat are the most common observable abnormalities in dogs with hypothyroidism. The classic cutaneous signs include bilaterally symmetric, non-pruritic truncal alopecia that tends to spare the head and extremities (Fig. 51-3). Alopecia may be local or generalized and symmetric or asymmetric, it may involve only the tail (i.e., "rat tail"), and it often initially starts over sites of wear

<sup>\*</sup>Odds of having serum thyroid hormone autoantibodies (THAA) among breeds with an increased risk of having THAA, compared with dogs of all other breeds.



BOX 51-2

# Clinical Manifestations of Hypothyroidism in the Adult Dog

#### Metabolic

Lethargy\*
Mental dullness\*
Inactivity\*
Weight gain\*
Cold intolerance

#### **Dermatologic**

Endocrine alopecia\*
Symmetric or asymmetric
"Rat tail"

Dry, brittle haircoat Hyperpigmentation

Séborrhea sicca or oleosa or dermatitis\* Pyoderma\* Otitis externa Myxedema

#### Reproductive

Persistent anestrus
Weak or silent estrus
Prolonged estrual bleeding
Inappropriate galactorrhea or gynecomastia
Testicular atrophy (?)
Loss of libido (?)

#### Neuromuscular

Weakness\* Knuckling Ataxia Circling Vestibular signs Facial nerve paralysis Seizures Laryngeal paralysis (?)

#### Ocular

Corneal lipid deposits Corneal ulceration Uveitis

#### Cardiovascular

Decreased contractility Bradycardia Cardiac arrythmias

#### **Gastrointestinal**

Esophageal hypomotility (?) Diarrhea Constipation

#### **Hematologic**

Anemia\*
Hyperlipidemia\*
Coagulopathy

Behavior Abnormalities (?)

and friction. Although nonpruritic endocrine alopecia is not pathognomonic for hypothyroidism (see Chapter 49), hypothyroidism is certainly the most likely diagnosis in an affected dog with lethargy, weight gain, and no polyuria-polydipsia.

Seborrhea and pyoderma are also common signs of hypothyroidism. Depletion of thyroid hormone suppresses humoral immune reactions, impairs T-cell function, and reduces the number of circulating lymphocytes—defects that can be reversed by exogenous thyroid hormone therapy. All forms of seborrhea (i.e., sicca, oleosa, dermatitis) are possible. Seborrhea and pyoderma may be focal, multifocal, or generalized. Because both frequently result in pruritus, hypothyroid dogs with secondary pyoderma or seborrhea may initially be brought to the veterinarian because of a pruritic skin disorder.

The haircoat in dogs with hypothyroidism is often dull, dry, and easily epilated. Hair regrowth is slow. Hyperkeratosis leads to the development of scales and dandruff. Variable degrees of hyperpigmentation may also be noted. Chronic otitis externa has been noted in some dogs with hypothyroidism. In severe cases of hypothyroidism acidic and neutral mucopolysaccharides may accumulate in the

dermis, bind water, and cause skin to thicken. Referred to as *myxedema*, the condition causes the skin to thicken predominantly in the forehead and face of dogs, resulting in rounding of the temporal region of the forehead, puffiness and thickening of the facial skin folds, and drooping of the upper eyelids.

# **NEUROMUSCULAR SIGNS**

Neurologic signs may be the predominant problem in some dogs with hypothyroidism (see Box 51-2). Hypothyroidism-induced segmental demyelination and axonopathy may cause signs referable to the central or peripheral nervous system. Clinical signs referable to the central nervous system (CNS) may also appear after mucopolysaccharide accumulates in the perineurium and endoneurium or after cerebral atherosclerosis, transient ischemia or brain infarctions, or the development of severe hyperlipidemia and include seizures, ataxia, circling, weakness, and proprioceptive and postural reaction deficits. These signs are often present in conjunction with vestibular signs (e.g., head tilt, nystagmus) or facial nerve paralysis. Peripheral neuropathies include facial nerve paralysis, weakness, and

<sup>\*</sup> Common.

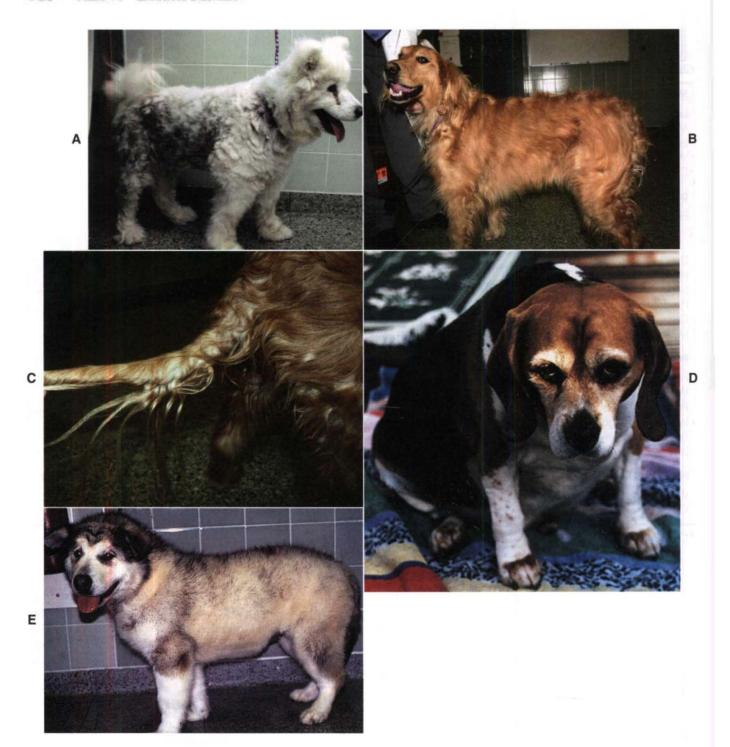


FIG 51-3

**A,** A 6-year-old female spayed Samoyed with hypothyroidism; a dry, lusterless haircoat; hyperpigmentation; and endocrine alopecia. **B** and **C,** A 2-year-old female spayed Golden Retriever with hypothyroidism, diffuse thinning of the haircoat, and development of a "rat tail." In both dogs note the truncal distribution of the dermatologic problem with sparing of the head and distal extremities. **D,** An 8-year-old male castrated Beagle with hypothyroidism, obesity, and myxedema of the face. Note the "tragic facial expression" and "mental dullness" evident from the dog's facial expression. **E,** A 7-month-old female Malamute with congenital hypothyroidism. Note the retention of the puppy haircoat and small stature of the dog.

knuckling or dragging of the feet, with excessive wear of the dorsal part of the toenail. Muscle wasting may also be evident, although myalgia is not common. Thyroxine-responsive unilateral forelimb lameness has also been observed in dogs. The relationship between hypothyroidism and laryngeal paralysis or esophageal hypomotility remains controversial, in part because it is difficult to prove a cause-and-effect relationship between these disorders and because treatment of hypothyroidism often does not improve the clinical signs caused by laryngeal paralysis or esophageal hypomotility.

#### REPRODUCTIVE SIGNS

Historically, hypothyroidism was believed to cause lack of libido, testicular atrophy, and oligospermia to azoospermia in male dogs. However, work by Johnson et al. (1999) in Beagles failed to document any deleterious effect of experimentally induced hypothyroidism on any aspect of male reproductive function. Although other classic clinical signs and clinicopathologic abnormalities of hypothyroidism developed in dogs studied, libido, testicular size, and total sperm count per ejaculate remained normal. These findings indicate that hypothyroidism may, at best, be an uncommon cause of reproductive dysfunction in male dogs, assuming that the Beagle is representative of other dog breeds.

Clinical experience has shown that hypothyroidism can cause prolonged interestrus intervals and failure to cycle in the bitch. Additional reproductive abnormalities include weak or silent estrous cycles, prolonged estrual bleeding (which may be caused by acquired problems in the coagulation system), and inappropriate galactorrhea and gynecomastia. An association between hypothyroidism and fetal resorption, abortion, and stillbirth has been suggested in the bitch; however, published documentation of this association is lacking. Maternal hypothyroidism has also been suggested to result in the birth of weak puppies that die shortly after birth.

# MISCELLANEOUS CLINICAL SIGNS

Ocular, cardiovascular, gastrointestinal, and clotting abnormalities are uncommon clinical manifestations of hypothyroidism (see Box 51-2). More commonly, biochemical or functional abnormalities of these organ systems are identified in dogs exhibiting the more common clinical signs of hypothyroidism. Echocardiography may identify a decrease in cardiac contractility that is usually mild and asymptomatic but that may become relevant during a surgical procedure requiring prolonged anesthesia and aggressive fluid therapy.

A reduction in the activity of factor VIII—related antigen (von Willebrand factor) activity has been inconsistently documented in dogs with hypothyroidism, and the development of clinical signs of a bleeding disorder in hypothyroid dogs is uncommon. An evaluation of the coagulation cascade or von Willebrand factor activity is not indicated in dogs with untreated hypothyroidism unless there are concurrent bleeding problems. Thyroid hormone supplementation has

a variable and sometimes deleterious effect on the blood concentration of von Willebrand factor in euthyroid dogs with von Willebrand's disease.

A cause-and-effect relationship between hypothyroidism and behavioral problems (e.g., aggression) has not been well established in dogs. To date, most reports have been anecdotal and based on improvement in behavior following initiation of thyroid hormone treatment. An inverse relationship between development of aggression and serotonin activity in the CNS has been documented in several species, including dogs. Serotonin turnover and sympathetic activity in the CNS increase in rats made hypothyroid after surgical thyroidectomy, dopamine receptor sensitivity is affected by thyroid hormone in rats, and thyroid hormone potentiates the activity of tricyclic antidepressants in humans suffering from certain types of depression. These studies suggest that thyroid hormone may have an influence on the serotonindopamine pathway in the CNS, regardless of the functional status of the thyroid gland. The benefits, if any, of using thyroid hormone to treat behavioral disorders such as aggression in dogs remain to be clarified.

## MYXEDEMA COMA

Myxedema coma is an uncommon syndrome of severe hypothyroidism characterized by profound weakness, hypothermia, bradycardia, and a diminished level of consciousness that can rapidly progress to stupor and then coma. Physical findings include profound weakness; hypothermia; nonpitting edema of the skin, face, and jowls (i.e., myxedema); bradycardia; hypotension; and hypoventilation. Laboratory findings may include hypoxemia, hypercarbia, hyponatremia, and hypoglycemia in addition to the typical findings of hyperlipidemia, hypercholesterolemia, and nonregenerative anemia. Serum thyroid hormone concentrations are usually extremely low or undetectable; serum TSH concentration is variable but typically increased. Treatment consists of intravenous levothyroxine (5 µg/kg q12h) and supportive care aimed at correcting hypothermia, hypovolemia, electrolyte disturbances, and hypoventilation. Once the dog has stabilized, oral levothyroxine can be started (see p. 741).

# **CRETINISM**

Hypothyroidism in puppies is termed *cretinism*. As the age of onset increases, the clinical appearance of animals with cretinism merges imperceptibly with that of adult hypothyroidism. Retarded growth and impaired mental development are the hallmarks of cretinism (Box 51-3). Dogs with cretinism have a disproportionate body size, with large, broad heads; thick, protruding tongues; wide, square trunks; and short limbs (Fig. 51-4). This is in contrast to the proportionate dwarfism caused by growth hormone deficiency. Cretins are mentally dull and lethargic and do not show the typical playfulness seen in normal puppies. Persistence of the puppy haircoat, alopecia, inappetence, delayed dental eruption, and goiter are additional signs. Differential diagnoses for failure to grow include endocrine (e.g., dwarfism) and nonendo-

crine causes (see Box 49-4 and Fig. 49-11). The presence of goiter is variable and dependent on the underlying etiology.

# AUTOIMMUNE POLYENDOCRINE SYNDROMES

Because autoimmune mechanisms play an important role in the pathogenesis of lymphocytic thyroiditis, it is not surpris-



BOX 51-3

#### Clinical Signs of Cretinism

Disproportionate dwarfism Short, broad skull Shortened mandible Enlarged cranium Shortened limbs Kyphosis Mental dullness Constipation Inappetence Gait abnormalities Delayed dental eruption Alopecia "Puppy haircoat" Dry hair Thick skin Lethargy Dyspnea Goiter

ing that lymphocytic thyroiditis may occur in conjunction with other immune-mediated endocrinopathies. Presumably, the immune-mediated attack is directed against antigens shared by the endocrine system. In human beings autoimmune polyglandular syndrome type II (Schmidt's syndrome) is the most common of the immunoendocrinopathy syndromes, and it usually consists of primary adrenal insufficiency, autoimmune thyroid disease, and type 1 diabetes mellitus. Autoimmune polyendocrine syndromes are uncommon in dogs and should be suspected in a dog found to have multiple endocrine gland failure. Hypothyroidism; hypoadrenocorticism; and, to a lesser extent, diabetes mellitus, hypoparathyroidism, and lymphocytic orchitis are recognized combined syndromes. In most affected dogs each endocrinopathy is manifested separately, with additional disorders ensuing one by one after variable periods (months to years). Diagnostic tests and treatment are directed at each disorder as it is recognized because it is not possible to reliably predict or prevent any of these problems. Immunosuppressive drug therapy is not indicated for animals with these syndromes because the adverse effects of immunosuppressive therapy and the difficulty posed by suppression of the immune destruction of affected endocrine glands outweigh the potential benefits of such therapy.

# Clinical Pathology

The most consistent clinicopathologic findings in dogs with hypothyroidism are hypercholesterolemia and hypertriglyceridemia; the latter is identified as lipemia. Hypercholesterolemia is identified in approximately 75% of hypothyroid dogs, and the cholesterol concentration can exceed 1000 mg/





A and **B,** Eight-month-old female Giant Schnauzer litter mates. The dog on the left is normal, whereas the smaller dog on the right has congenital hypothyroidism (cretinism). Note the small stature; disproportionate body size; large, broad head; wide, square trunk; and short limbs in the cretin. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

В

dl. Although fasting hypercholesterolemia and hypertriglyceridemia can be associated with several other disorders (see Chapter 54), their presence in a dog with appropriate clinical signs is strong evidence for hypothyroidism.

A mild normocytic, normochromic, nonregenerative anemia (packed cell volume [PCV] of 28% to 35%) is a less consistent finding. Evaluation of red blood cell morphology may reveal an increase in the numbers of leptocytes (target cells), which develop as a result of increased erythrocyte membrane cholesterol loading. The white blood cell count is typically normal, and platelet counts are normal to increased.

A mild to moderate increase in lactate dehydrogenase; aspartate aminotransferase; alanine transaminase; alkaline phosphatase; and, rarely, creatine kinase activities may be identified but are extremely inconsistent findings and may not be directly related to the hypothyroid state. Mild hypercalcemia may be found in some dogs with congenital hypothyroidism. Results of urinalysis are usually normal. Polyuria, hyposthenuria, and urinary tract infections are not typical of hypothyroidism.

#### **DERMATOHISTOPATHOLOGIC FINDINGS**

Skin biopsies are often performed in dogs with suspected endocrine alopecia, especially if screening diagnostic tests (including tests to assess thyroid gland function) have failed to identify the cause. Nonspecific histologic changes are associated with various endocrinopathies, including hypothyroidism (see Table 49-5); histologic alterations that are claimed to be specific to hypothyroidism may also be seen, including vacuolated and/or hypertrophied arrector pili muscles, increased dermal mucin content, and thickened dermis. A variable inflammatory cell infiltrate may be present if a secondary pyoderma has developed.

#### **ULTRASONOGRAPHIC FINDINGS**

Ultrasound evaluation of the thyroid lobe may be helpful in differentiating dogs with hypothyroidism from euthyroid dogs with nonthyroidal illness causing low thyroid hormone test results. Lymphocytic thyroiditis and idiopathic atrophy eventually cause a decrease in the size and alterations in the echogenicity of the thyroid lobe. The thyroid lobe in euthyroid dogs is usually fusiform and triangular to oval in shape on longitudinal and transverse views, respectively; has a homogeneous echogenic pattern; is hyperechoic to isoechoic, compared with the echogenicity of the surrounding musculature; and has a hyperechoic capsule (Fig. 51-5). Although thyroid lobe shape is often similar between euthyroid and hypothyroid dogs, there is often a significant reduction in size and volume of the thyroid lobe in hypothyroid versus euthyroid dogs. In addition, the echogenicity of the thyroid lobe in hypothyroid dogs tends to be isoechoic to hypoechoic with hyperechoic foci, and the echogenic pattern often differs between thyroid lobes in the same dog. A direct correlation between size of the dog and size and volume of the normal thyroid gland may exist; the smaller the dog, the smaller the size and volume of the thyroid lobe (Fig. 51-6). This must be considered when evaluating thyroid lobe size in a dog with suspected hypothyroidism.

# **TESTS OF THYROID GLAND FUNCTION**Overview

Function of the thyroid gland is typically assessed by measuring baseline serum thyroid hormone concentrations. 3,5,3'5'-tetraiodothyronine (thyroxine  $[T_4]$ ) accounts for most of the thyroid hormone secreted by the thyroid gland, with only small quantities of 3,5,3'-triiodothyronine  $(T_3)$  and minor amounts of 3,3',5'-triiodothyronine (reverse  $T_3$   $[rT_3]$ ) released. Once secreted into the circulation, more than

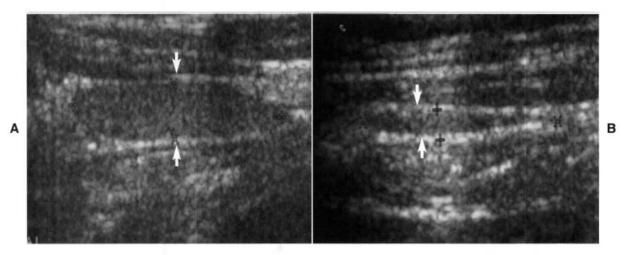


FIG 51-5

**A,** Ultrasound image of the normal-appearing left thyroid lobe (arrows) of a healthy adult Golden Retriever. **B,** Ultrasound image of the left thyroid lobe (arrows) of an adult Golden Retriever dog with primary hypothyroidism. Note the significant reduction in the size of the thyroid lobe in the dog with hypothyroidism, compared with the thyroid lobe image from the healthy dog.

99% of  $T_4$  is bound to plasma proteins, which serves as a reservoir and buffer to maintain a steady concentration of free  $T_4$  ( $fT_4$ ) in the plasma. The unbound, or free,  $T_4$  is biologically active, exerts negative feedback inhibition on pituitary TSH secretion (see Fig. 51-1), and is capable of entering cells throughout the body (Fig. 51-7). Within the cell  $fT_4$  is

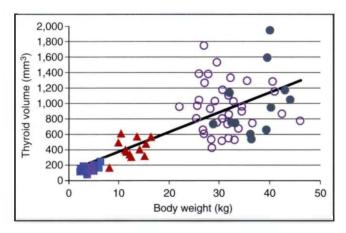


FIG 51-6

The relationship between total thyroid gland volume determined by ultrasound and body weight in 12 healthy Akitas (closed circles), 36 Golden Retrievers (open circles), 12 Beagles (triangles), and 12 Miniature and Toy Poodles (squares). Notice the positive correlation between body weight and size of the thyroid gland. (From Bromel C et al: Comparison of ultrasonographic characteristics of the thyroid gland in healthy small-, medium-, and large-breed dogs, Am J Vet Res 67:70, 2006.)

deiodinated to form either  $T_3$  or  $rT_3$ , depending on the metabolic demands of the tissues at that particular time.  $T_3$  is preferentially produced during normal metabolic states;  $rT_3$ , is biologically inactive.  $T_3$  is believed to be the primary hormone that induces physiologic effects.

All serum T<sub>4</sub>, both protein bound and free, comes from the thyroid gland. Therefore tests that measure the serum total and fT<sub>4</sub> concentrations, in conjunction with the serum TSH concentration, are currently recommended for the assessment of thyroid gland function in dogs suspected of having hypothyroidism. Serum T<sub>3</sub> concentration is a poor gauge of thyroid gland function because of its predominant location within cells and the minimal amount secreted by the thyroid gland in comparison with the amount of T<sub>4</sub> secreted (Fig. 51-8). Thus measurement of serum T<sub>3</sub>, free T<sub>3</sub>, and rT<sub>3</sub> concentration is not recommended for assessing thyroid gland function in dogs.

#### Baseline Serum T<sub>4</sub> Concentration

The baseline serum  $T_4$  concentration is the sum of the protein-bound and free levels circulating in the blood. Measurement of serum  $T_4$  concentration can be the initial screening test for hypothyroidism or be part of a thyroid panel containing  $T_4$ ,  $fT_4$ , TSH, an antibody test for lymphocytic thyroiditis, or some combination of these tests (Box 51-4).

Clinical chemistry laboratories currently use a radioimmunoassay (RIA) technique or enzyme immunoassay for measuring serum T<sub>4</sub>. Point-of-care ELISAs for measuring serum T<sub>4</sub> are also available, are economical, quick, and easy to perform, and allow the clinician to make recommendations the same day the dog (or cat) is evaluated. In a recent

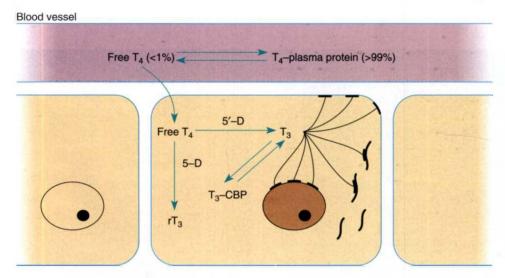


FIG 51-7

Intracellular metabolism of free T<sub>4</sub> to either T<sub>3</sub> or reverse T<sub>3</sub> by 5'- or 5-monodeiodinase, respectively. Intracellular T<sub>3</sub> formed from monodeiodination of free T<sub>4</sub> can interact with T<sub>3</sub> receptors on the cell membrane, mitochondria, or nucleus of the cell and stimulate the physiologic actions of thyroid hormone or bind to cytoplasmic binding proteins (CBP). The latter form an intracellular storage pool for T<sub>3</sub>. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

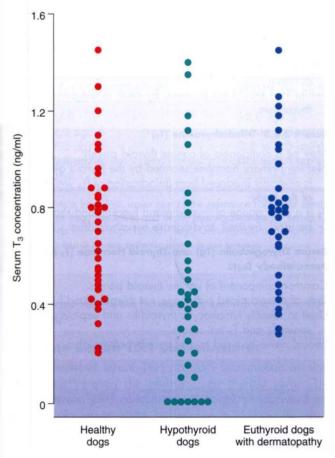


FIG 51-8
Baseline serum  $T_3$  concentrations in 35 healthy dogs, 35 dogs with hypothyroidism, and 30 euthyroid dogs with concurrent dermatopathy. Note the overlap in serum  $T_3$  concentrations among the three groups of dogs.

study serum  $T_4$  concentrations determined in dogs and cats by RIA, chemiluminescent enzyme immunoassay, and a point-of-care ELISA provided similar and consistent results (Kemppainen and Birchfield, 2006). For most laboratories the lower limit of the reference range for serum  $T_4$  in dogs is approximately 0.8 to 1.0  $\mu$ g/dl (10 to 13 nmol/L), although in some breeds the normal range may extend to as low as 0.5  $\mu$ g/dl (6 nmol/L) (see the discussion of breed variations, p. 740).

Theoretically, the interpretation of baseline serum  $T_4$  concentration should be straightforward in that dogs with hypothyroidism should have low values compared with the values in healthy dogs. Unfortunately, the serum  $T_4$  concentration range in hypothyroid dogs overlaps with that in healthy dogs and the serum  $T_4$  concentration can be suppressed by a variety of factors, most notably nonthyroidal illness and medications (Table 51-2). Clinicians often find it difficult to judge the effect that extraneous factors, especially concurrent illness, have on the serum  $T_4$  concentration. Because these variables can suppress a baseline serum  $T_4$  concentration to less than  $0.5 \mu g/dl$  in a euthyroid dog and hypothyroid dogs rarely have a serum  $T_4$  concentration

greater than 1.5 | g/dl, the serum T<sub>4</sub> concentration should be used to confirm normal thyroid gland function, not hypothyroidism per se (Table 51-3). A serum T<sub>4</sub> concentration greater than 1.5 µg/dl establishes normal thyroid gland function. The exception is a very small number (<1%) of hypothyroid dogs with lymphocytic thyroiditis that have serum T<sub>4</sub> autoantibodies that interfere with the RIA used to measure  $T_4$ . A serum  $T_4$  concentration less than 0.5  $\mu$  g/dl (6 nmol/L) suggests hypothyroidism, especially if the clinical signs, physical findings, and results of routine blood tests support the diagnosis and systemic illness is not present. The definitive diagnosis relies on response to trial therapy with levothyroxine in these dogs. Additional diagnostic tests of thyroid gland function are indicated if the serum T4 concentration is between 0.5 and 1.5 µg/dl; if the clinical signs, physical examination findings, and results of routine blood work are not strongly supportive of the disease; if severe systemic illness is present and the potential for the euthyroid sick syndrome is high; or if medications known to decrease serum T<sub>4</sub> concentration are being administered.

#### Baseline Serum fT<sub>4</sub> Concentration

Free T<sub>4</sub> is the nonprotein-bound fraction of T<sub>4</sub> circulating in blood and accounts for less than 1% of circulating T<sub>4</sub>. Currently, the most commonly used assays for measuring fT<sub>4</sub> in dogs are the Nichol's modified equilibrium dialysis assay (Antech Diagnostics, Inc.) and the Diasorin 2-step assay (Diasorin, Stillwater, Minn.). The modified equilibrium dialysis (ED) assay utilizes a short ED step to separate free from protein-bound T<sub>4</sub> followed by measurement of the free T<sub>4</sub> fraction by RIA. The Diasorin 2-step fT<sub>4</sub> assay uses two incubation temperatures (37° C for 20 minutes, then room temperature for 1 hour), not ED, to separate free and proteinbound T<sub>4</sub> followed by RIA to measure fT<sub>4</sub>. Preliminary studies suggest that results using the Diasorin 2-step RIA method are similar to results using the more traditional ED method. For most laboratories the lower limit of the reference range for serum fT<sub>4</sub> measured by ED and the 2-step RIA is approximately 0.5 to 0.8 ng/dl (6 to 10 pmol/L) in dogs.

Measurement of serum fT<sub>4</sub> is usually reserved for those dogs with suspected hypothyroidism and a nondiagnostic serum T<sub>4</sub> test result, severe concurrent illness, or both. ED assays for serum fT<sub>4</sub> concentration have comparable sensitivity but higher specificity than assays for serum T<sub>4</sub> concentration. Similar studies have not been reported for the 2-step RIA. Serum fT<sub>4</sub> is more resistant to the suppressive effects of nonthyroidal illness and medications than serum T<sub>4</sub>, although severe illness can cause serum fT<sub>4</sub> concentrations to decrease below 0.5 ng/dl. In addition, serum T<sub>4</sub> autoantibodies do not affect serum fT<sub>4</sub> results determined by ED. Interpretation of serum fT<sub>4</sub> test results is similar to that used to interpret serum T<sub>4</sub> test results (see Table 51-3). Serum fT<sub>4</sub> values greater than 1.5 ng/dl (20 pmol/L) are consistent with euthyroidism; values less than 0.5 ng/dl (6.5 pmol/L) are supportive of hypothyroidism, assuming the history, physical examination, and results of routine blood work are consistent with hypothyroidism and severe systemic illness is



#### Diagnostic Tests for Evaluating Thyroid Gland Function in the Dog

The decision to assess thyroid gland function should be based on results of the history, physical examination, and results of routine blood work (complete blood count, serum biochemistry panel, urinalysis).

#### Serum Thyroxine (T<sub>4</sub>)

Most commonly used initial screening test for hypothyroidism Normal serum  $T_4$  rules out hypothyroidism

Exception: T<sub>4</sub> autoantibodies that interfere with T<sub>4</sub> assay and cause spuriously high results (uncommon)

Low serum T<sub>4</sub> does not, by itself, confirm hypothyroidism Serum T<sub>4</sub> commonly suppressed below the reference range by nonthyroidal illness, drugs, and other factors in dogs with normal thyroid gland function

#### Serum Free Thyroxine (FT<sub>4</sub>) By Dialysis

Usually measured in dogs with nondiagnostic serum T<sub>4</sub> test results, severe nonthyroidal illness, or both; common component of canine thyroid panels

Normal serum fT<sub>4</sub> rules out hypothyroidism

Low serum fT<sub>4</sub> does not, by itself, confirm hypothyroidism; severe nonthyroidal illness and drugs can suppress serum fT<sub>4</sub> to below the reference range

#### Serum Thyrotropin (TSH)

Usually measured in dogs with nondiagnostic serum T<sub>4</sub> test results, severe nonthyroidal illness, or both; common component of canine thyroid panels

Provides additional evidence for or against the diagnosis of hypothyroidism

False positive and false negative serum TSH test results are common

Serum TSH should not be used, by itself, to diagnose hypothyroidism

#### Serum 3,5,3'-Triiodothyronine (T<sub>3</sub>)

May be a component of canine thyroid panels

Not the primary hormone secreted by the thyroid gland; T<sub>3</sub> is primarily produced from deiodination of fT<sub>4</sub> within cells of the body

T<sub>3</sub> is a poor gauge of thyroid gland function and should not be used, by itself, to diagnose hypothyroidism

#### Serum Thyroglobulin (Tg) and Thyroid Hormone ( $T_3$ and $T_4$ ) Autoantibody Tests

Common component of canine thyroid panels
Tests of thyroid gland pathology, not thyroid gland function
Used to identify lymphocytic thyroiditis and explain unusual serum T<sub>4</sub> and T<sub>3</sub> test results

Should never be used to diagnose hypothyroidism



**TABLE 51-2** 

Variables that May Affect Baseline Serum Thyroid Hormone Function Test Results in the Dog

Inversely proportional effect
Increased T <sub>4</sub>
Decreased T <sub>4</sub>
Inversely proportional effect
Increased T <sub>4</sub>
Decreased T <sub>4</sub>
Decreused 14
T <sub>4</sub> and free T <sub>4</sub> lower than normal range established for dogs; no difference for TSH
14 and nee 14 lower man formal range established for dogs, no unforcince for fort
No effect
No effect
Increased
Decreased $T_4$ , no effect on free $T_4$
Increased $T_4$ , decreased TSH, no effect on free $T_4$
No effect on $T_4$
Increased T <sub>4</sub>
Decreased T <sub>4</sub>
Decreased $T_4$ and free $T_4$ ; depending on illness, TSH may increase, decrease or
not change
No effect on T <sub>4</sub> , free T <sub>4</sub> , or TSH
See Table 51-4
If excessive, decreased T <sub>4</sub> and free T <sub>4</sub> ; increased TSH
Increased or decreased $T_4$ ; no effect on free $T_4$ or TSH

TSH, Thyroid-stimulating hormone.

<sup>\*</sup>There is a direct correlation between the severity and systemic nature of the illness and suppression of serum T<sub>4</sub> and free T<sub>4</sub> concentrations.



**TABLE 51-3** 

Interpretation of Baseline Serum Thyroxine ( $T_4$ ) and Free Thyroxine ( $fT_4$ ) Concentration in Dogs with Suspected Hypothyroidism\*

SERUM T4 CONCENTRATION	SERUM FT4 CONCENTRATION	PROBABILITY OF HYPOTHYROIDISM
>2.0 µg/dl	>2.0 ng/dl	Very unlikely
1.5 to 2.0 μg/dl	1.5 to 2.0 ng/dl	Unlikely
0.8 to 1.5 μg/dl	0.8 to 1.5 ng/dl	Unknown
0.5 to 0.8 μg/dl	0.5 to 0.8 ng/dl	Possible
<0.5 μg/dl	<0.5 ng/dl	Very likely <sup>†</sup>

<sup>\*</sup>Interpretation based on lower end of the reference range for serum  $T_4$  and  $fT_4$  being 0.8  $\mu$ g/dl and 0.8  $\eta$ g/dl, respectively, without regard for breed of dog. The lower end of the reference range for serum  $T_4$  and  $fT_4$  may be as low as 0.5  $\mu$ g/dl and 0.5  $\eta$ g/dl, respectively, for some breeds such as sight hounds (e.g., Greyhounds) and Nordic breeds (e.g., Siberian Huskies).

not present; and values between 0.5 and 1.5 ng/dl are not diagnostic.

#### **Baseline Serum TSH Concentration**

Measurement of serum TSH provides information on the interaction between the pituitary and thyroid gland. In theory, serum TSH concentration should be increased in dogs with hypothyroidism. In dogs serum TSH can be measured using immunoradiometric, chemiluminescent immunometric, and enzyme immunometric assays. In one study the highest precision for canine TSH analysis was obtained with the chemiluminescent assay, although the correlation between the three assays for measuring canine serum TSH was satisfactory (Marca et al., 2001). Most clinical laboratories use a serum TSH concentration of 0.6 ng/ml as the upper limit of the reference range. The lower limit of the reference range is currently below the sensitivity of these assays; differentiation between low and normal serum TSH concentrations is not possible.

Measurement of serum TSH concentration is usually reserved for dogs with suspected hypothyroidism and nondiagnostic serum T4 test results. A serum TSH concentration greater than 0.6 ng/ml is consistent with hypothyroidism. Unfortunately, serum TSH concentrations can be normal in dogs with histologically confirmed hypothyroidism and increased in euthyroid dogs with concurrent nonthyroidal illness or dogs receiving drugs such as phenobarbital (Fig. 51-9). In most studies the sensitivity and specificity of the TSH assay has ranged from 63% to 87% and 82% to 93%, respectively. Serum TSH test results should always be interpreted in conjunction with results of serum T4, fT4, or both and should not be used alone in the diagnosis of hypothyroidism. Serum TSH test results increase the likelihood of euthyroidism or hypothyroidism when results are consistent with results of serum T4 and fT4 tests. A normal serum T4 and fT4 concentration and increased serum TSH concentration occur in the early stages of primary hypothyroidism in humans. Although similar thyroid hormone and TSH test results have been identified in dogs, it is not known what percentage of these dogs progress to clinical hypothyroidism. Clinical signs of hypothyroidism are usually not evident in these dogs, presumably because serum  $T_4$  and  $fT_4$  concentrations are in the reference range. Treatment with levothyroxine is not indicated. Rather, assessment of thyroid gland function should be repeated in 3 to 6 months, especially if antibody tests for lymphocytic thyroiditis are positive. If progressive destruction of the thyroid gland is occurring, serum  $T_4$  and  $fT_4$  concentrations will gradually decrease and clinical signs will eventually develop.

#### **TSH and TRH Stimulation Tests**

TSH and TRH stimulation tests evaluate the thyroid gland's responsiveness to exogenous TSH and TRH administration, respectively. The primary advantage of these tests is that they help differentiate between hypothyroidism and nonthyroidal illness in dogs with low serum  $T_4$  and  $fT_4$  concentrations. Unfortunately, TRH for injection is currently not available. Recombinant human TSH (rhTSH) for injection is effective in stimulating thyroid hormone secretion in dogs but is not available at a reasonable cost. The current TSH stimulation protocol for dogs is 75 ug of rhTSH per dog administered intravenously or intramuscularly and blood for serum T4 concentration obtained before and 6 hours after rhTSH administration. In a euthyroid dog serum T<sub>4</sub> concentration should be ≥ 2.5 µg/dl (30 nmol/L) 6 hours after rhTSH administration and the 6-hour post-rhTSH serum T4 concentration should be ≥1.5 times the baseline serum T<sub>4</sub> concentration. Reconstituted rhTSH can be stored at 4° C for 4 weeks and at -20° C for 8 weeks without loss of biological activity.

#### **Antibody Tests for Lymphocytic Thyroiditis**

Circulating thyroglobulin (Tg) and thyroid hormone ( $T_3$  and  $T_4$ ) autoantibodies correlate with the presence of lymphocytic thyroiditis in dogs. Tests for the presence of Tg,  $T_3$ , and  $T_4$  autoantibodies in the serum of dogs can be used to identify lymphocytic thyroiditis, to explain unusual serum

<sup>&</sup>lt;sup>†</sup>Assuming that a severe systemic illness is not present.

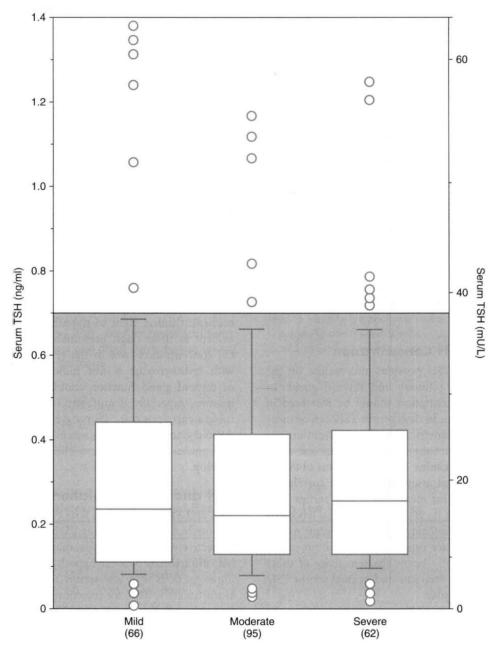


FIG 51-9

Box plots of serum concentrations of thyrotropin (TSH) in 223 dogs with nonthyroidal disease stratified according to severity of disease. For each box plot T-bars represent the main body of data, which in most instances is equal to the range. Each box represents an interquartile range (twenty-fifth to seventy-fifth percentile). The horizontal bar in each box is the median. Open circles represent outlying data points. Numbers in parentheses indicate the numbers of dogs in each group. Shaded area is the normal range. (From Kantrowitz LB et al: Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease, J Am Vet Med Assoc 219:765, 2001.)

 $T_4$  test results, and possibly to serve as a genetic screening test for hypothyroidism caused by lymphocytic thyroiditis. Autoantibodies predominantly develop against Tg.  $T_3$  and  $T_4$  are haptens and not antigenic by themselves. Tg is the protein that provides the antigenic stimulus. Because  $T_3$  and  $T_4$  are attached to the Tg molecule, autoantibodies develop

against them as well. Dogs with  $T_3$  and  $T_4$  autoantibodies typically have autoantibodies against Tg, but the converse is not true. As such, the better screening test for lymphocytic thyroiditis is the Tg autoantibody test. ELISAs for detection of Tg autoantibodies are sensitive and specific for identification of Tg autoantibodies in dogs and are commercially

available. Results are reported as negative, positive, and inconclusive.

A positive Tg autoantibody test suggests the possibility of lymphocytic thyroiditis but does not provide information on the severity or progressive nature of the inflammatory process. Tg autoantibody is not a thyroid function test. Positive results increase the suspicion for hypothyroidism if serum  $T_4$  and  $fT_4$  concentrations are low but have no bearing on generation of clinical signs if serum T4 and fT4 concentrations are normal. Tg autoantibodies should not be used alone in the diagnosis of hypothyroidism. Dogs with confirmed hypothyroidism can be negative and euthyroid dogs can be positive for Tg autoantibodies. Identification of Tg autoantibodies would support hypothyroidism caused by lymphocytic thyroiditis if the dog has clinical signs, physical findings, and thyroid hormone test results consistent with the disorder. Positive serum T4 and T3 autoantibody test results are interpreted in a similar manner.

The value of serum Tg autoantibodies as a marker for eventual development of hypothyroidism remains to be clarified. A 1-year prospective study found that approximately 20% of 171 dogs with positive Tg autoantibody and normal  $f\Gamma_4$  and TSH test results developed changes in  $f\Gamma_4$ , TSH, or both test results consistent with hypothyroidism; 15% reverted to a negative Tg autoantibody test with no change in  $f\Gamma_4$  and TSH test results; and 65% remained Tg autoantibody positive or had an inconclusive result with no change in  $f\Gamma_4$  and TSH test results 1 year later (Graham et al., 2001). Currently, a positive Tg autoantibody test is considered suggestive of lymphocytic thyroiditis and supports retesting thyroid gland function in 3 to 6 months.

Testing for serum T<sub>4</sub> or Tg autoantibodies is indicated in dogs with unusual serum T4 values. T4 autoantibodies may interfere with the RIAs used to measure serum T4 concentrations, which thereby yield spurious and thus unreliable values. The type of interference depends on the separation system used in the RIA. Falsely low results are obtained if nonspecific separation methods are used (e.g., ammonium sulfate, activated charcoal); falsely increased values are obtained if single-step separation systems using antibodycoated tubes are used. Fortunately, spurious T4 values resulting from clinically relevant concentrations of thyroid hormone antibody account for less than 1% of such results from commercial endocrine laboratories. Serum fT4 measured using an ED technique is not affected by T4 autoantibodies and should be evaluated in lieu of serum T4 in dogs suspected of having  $T_4$  autoantibodies.

# FACTORS AFFECTING THYROID GLAND FUNCTION TESTS

There are many factors that affect baseline thyroid hormone and endogenous TSH concentrations (see Table 51-2). Unfortunately, most of these factors decrease baseline thyroid hormone concentrations and may increase endogenous TSH in euthyroid dogs, potentially causing misdiagnosis of hypothyroidism if the clinician accepts the results out of context.

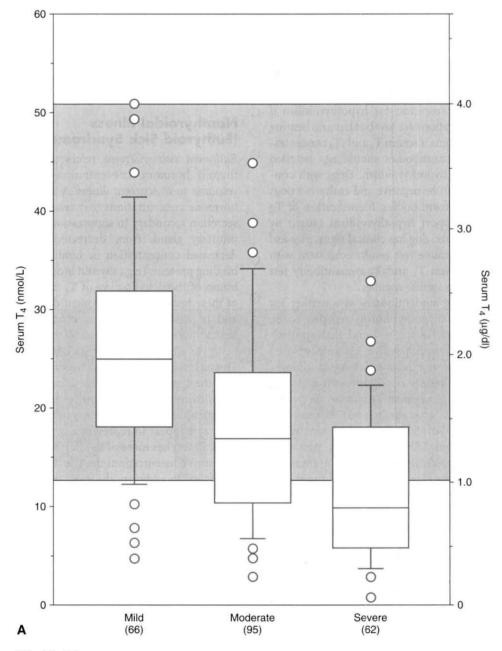
The most common factors that result in lower baseline thyroid hormone concentrations in euthyroid dogs are non-thyroidal illness (i.e., euthyroid sick syndrome), drugs (especially glucocorticoids, phenobarbital, and sulfonamide antibiotics; see Table 51-2), and variation in the reference range between breeds (most notably sight hounds).

#### Nonthyroidal Illness (Euthyroid Sick Syndrome)

Euthyroid sick syndrome refers to suppression of serum thyroid hormone concentrations in euthyroid dogs in response to concurrent illness. A decrease in serum thyroid hormone concentrations may result from a decline in TSH secretion secondary to suppression of the hypothalamus or pituitary gland, from decreased synthesis of T4, from decreased concentration or binding affinity of circulating binding proteins (e.g., thyroid binding globulin), from inhibition of the deiodination of T<sub>4</sub> to T<sub>3</sub>, or any combination of these factors. The subsequent decrease in serum total T<sub>4</sub> and, in many cases, fT<sub>4</sub> concentrations is believed to represent a physiologic adaptation by the body, with the purpose being to decrease cellular metabolism during periods of illness. It is not indicative of hypothyroidism, per se. Generally, the type and magnitude of most alterations in serum thyroid hormone concentrations are not unique to a specific disorder but reflect the severity of the illness or the catabolic state and appear to represent a continuum of changes. Systemic illness has more of an effect in lowering serum thyroid hormone concentrations than do, for example, dermatologic disorders. In addition, the more severe the systemic illness, the more suppressive the effect on the serum thyroid hormone concentration (Fig. 51-10).

Unfortunately, euthyroid dogs with concurrent illness can have serum T<sub>4</sub> concentrations that often fall between 0.5 and 1.0 µg/dl, and with severe illness (e.g., cardiomyopathy, severe anemia) these concentrations can be less than 0.5 µg/ dl. Alterations in serum concentrations of fT4 and TSH are more variable and probably depend in part on the pathophysiologic mechanisms involved in the illness. In general, serum fT4 concentrations tend to be decreased in dogs with concurrent illness but to a lesser extent than total T<sub>4</sub> concentrations. However, fT<sub>4</sub> concentrations can be less than 0.5 ng/ dl if severe illness is present. TSH concentrations may be normal or increased depending, in part, on the effect of the concurrent illness on  $f\Gamma_4$  concentrations and on pituitary function. If pituitary function is suppressed, TSH concentrations will be in the normal range or undetectable. If pituitary response to changes in fT4 concentration is not affected by the concurrent illness, TSH concentrations will increase in response to a decrease in fT<sub>4</sub>. Serum TSH concentrations can easily exceed 1.0 ng/ml in dogs with euthyroid sick

Treatment of euthyroid sick syndrome should be aimed at the concurrent illness. The serum thyroid hormone concentrations return to normal once the concurrent illness is eliminated. Treatment of euthyroid sick syndrome with sodium levothyroxine is not recommended.



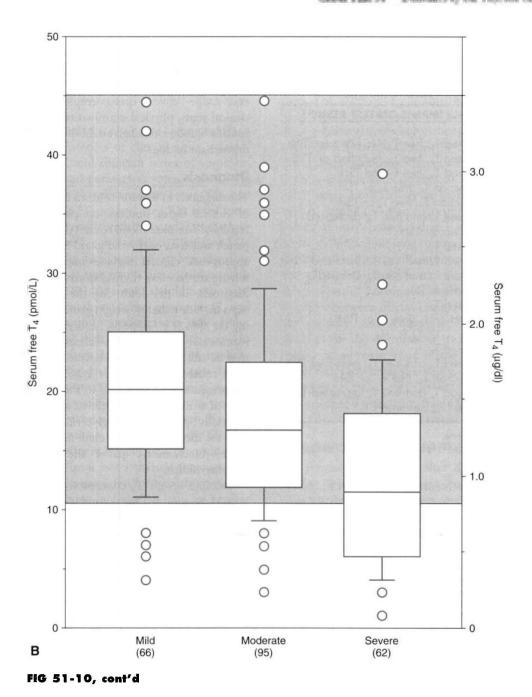
**FIG 51-10** Box plots of serum total  $T_4$  (A) and free  $T_4$  (B) concentrations in 223 dogs with nonthyroidal disease stratified according to severity of disease. See Fig. 51-9 for explanation. (From Kantrowitz LB et al: Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease, *J Am Vet Med Assoc* 219:765, 2001.)

#### Drugs

Clinical knowledge of the effect, if any, of various drugs and hormones on serum thyroid hormone and TSH concentrations in dogs is expanding as investigators continue to examine the interplay between medications and thyroid hormone test results (Table 51-4). As a general rule, any drug should be suspected of affecting thyroid hormone test results, especially if the history, clinical signs, and clinicopathologic

abnormalities do not support a diagnosis of hypothyroidism. Glucocorticoids, phenobarbital and sulfonamides are the most commonly used drugs known to affect serum thyroid hormone test results.

**Glucocorticoids.** Glucocorticoids cause a decrease in serum  $T_4$  and  $fT_4$  concentrations. Serum TSH concentration is variable but usually within the reference range. The magnitude and duration of suppression of serum thyroid



hormone concentrations depend on the type of glucocorticoid, dosage, route of administration, and duration of glucocorticoid administration. The higher the dosage, the longer the administration, and the more potent the glucocorticoid administered, the more severe the suppression of serum thyroid hormone concentrations. If glucocorticoids have been administered in the recent past, assay of serum thyroid hormone concentrations should be delayed or must be interpreted carefully. Ideally, glucocorticoids should be discontinued and serum thyroid hormone and TSH concentrations

Typically, the administration of exogenous glucocorticoids does not result in clinical signs of hypothyroidism. The

assessed 4 to 8 weeks later.

exception are dogs receiving relatively high dosages of glucocorticoids for prolonged periods to treat chronic steroidresponsive disorders (e.g., immune-mediated diseases). In these dogs glucocorticoid-induced secondary hypothyroidism may become clinical and require treatment with synthetic levothyroxine.

**Phenobarbital.** In dogs phenobarbital treatment at therapeutic dosages decreases serum  $T_4$  and  $fT_4$  concentrations into the range consistent with hypothyroidism. A delayed increase in the serum TSH concentration may occur secondary to loss of negative feedback as serum  $T_4$  and  $fT_4$  concentrations decline. Increased serum TSH concentrations quickly return to the reference range after discontinu-



Drugs that May Affect Baseline Serum Thyroid Hormone Function Test Results in the Dog

#### DRUG **POSSIBLE IMPACT ON TEST RESULTS** Aspirin Decreased T<sub>4</sub>, free T<sub>4</sub>; No effect on TSH Clomipramine Decreased $T_4$ , free $T_4$ ; No effect on TSH Carprofen Decreased T<sub>4</sub>, free T<sub>4</sub> and TSH Deracoxib No effect on $T_4$ , free $T_4$ or TSH Etodolac No effect on T<sub>4</sub>, free T<sub>4</sub> or TSH Glucocorticoids Decreased T<sub>4</sub> and free T<sub>4</sub>; decreased or no effect on TSH Furosemide Decreased T<sub>4</sub> Methimazole Decreased T<sub>4</sub> and free T<sub>4</sub>; increased TSH Decreased T<sub>4</sub> and free T<sub>4</sub>; Delayed **Phenobarbital** increase in TSH Phenylbutazone Decreased T<sub>4</sub> No effect on T<sub>4</sub>, free T<sub>4</sub> or TSH Potassium bromide **Progestagens** Decreased T<sub>4</sub> Propylthiouracil Decreased T<sub>4</sub> and free T<sub>4</sub>; increased TSH Cephalexine No effect on T<sub>4</sub>, free T<sub>4</sub>, or TSH Sulfonamides Decreased T<sub>4</sub> and free T<sub>4</sub>; increased TSH **Ipodate** Increased T<sub>4</sub>, decreased T<sub>3</sub>

TSH, Thyroid-stimulating hormone.

ation of phenobarbital treatment, whereas serum  $T_4$  and  $fT_4$  concentrations may take up to 4 weeks to return to pretreatment values. Potassium bromide treatment does not seem to have a significant effect on serum  $T_4$ ,  $fT_4$  and TSH concentrations in dogs.

**Sulfonamide antibiotics.** A decrease in serum  $T_4$  and  $fT_4$  and an increase in TSH concentrations have been documented in dogs treated with sulfonamides (e.g., sulfamethoxazole, sulfadiazine). Serum  $T_4$  concentrations can decrease into the hypothyroid range within 1 to 2 weeks and serum TSH concentrations can increase above the reference range within 2 to 3 weeks after initiating sulfonamide therapy. Clinical signs of hypothyroidism can develop with chronic sulfonamide administration. The increase in the serum TSH concentration occurs secondary to loss of negative feedback as serum  $T_4$  and  $fT_4$  concentrations decline and can lead to thyroid hyperplasia and goiter. Alterations in results of thyroid gland function tests may resolve within 1 to 2 weeks or last as long as 8 to 12 weeks after cessation of the antibiotic.

#### **Breed Variations**

Current reference ranges were established in large populations of dogs without regard for breed. It is now recognized that the reference range for serum  $T_4$  and  $fT_4$  concentration but not TSH concentration is lower in sight hounds, most notably Greyhounds, and Northern breeds such as the Siberian Husky and may be lower in other breeds as well. The lower end of the reference range for serum  $T_4$  and  $fT_4$  in these

breeds may be as low as  $0.4 \,\mu\text{g/dl}$  and  $0.4 \,\text{ng/dl}$ , respectively. Serum  $T_4$  and  $fT_4$  concentrations that are consistent with hypothyroidism according to standard reference ranges may actually be normal in these breeds. Differences in the reference range between breeds emphasizes the importance of clinical signs, physical examination findings, and results of routine blood work when establishing the diagnosis of hypothyroidism in dogs.

#### Diagnosis

The diagnosis of hypothyroidism is based on a combination of clinical signs; findings on physical examination; and results of complete blood count (CBC), serum biochemistry panel, and tests of thyroid gland function. The presence of appropriate clinical signs is imperative, especially when relying on baseline thyroid hormone concentrations for a diagnosis. In the adult dog the most consistent clinical signs include lethargy, weight gain, and abnormalities affecting the skin (e.g., alopecia, seborrhea, pyoderma) and neuromuscular system (e.g., weakness). Other organ systems may be affected by thyroid hormone deficiency, but clinical signs related to these other systems are rarely the reason for presentation of the dog to the veterinarian. Identification of a mild nonregenerative anemia on the CBC and especially lipemia (hypertriglyceridemia) in the blood sample and an increased serum cholesterol concentration on a serum biochemistry panel adds further evidence for hypothyroidism.

Baseline serum T<sub>4</sub> concentration is often used as the initial screening test for thyroid gland function. It is important to remember that serum T4 concentrations can be suppressed by a variety of factors, most notably nonthyroidal illness and medications such as prednisone and phenobarbital. As such, measurement of the serum T<sub>4</sub> concentration should be used to confirm normal thyroid gland function, not hypothyroidism per se. A normal serum T4 concentration establishes normal thyroid gland function unless serum  $T_4$  autoantibodies are present and interfering with the assay. A low serum T<sub>4</sub> concentration (ideally less than 0.5 µg/dl [6 nmol/L]) in conjunction with hypercholesterolemia and clinical signs strongly suggestive of the disease supports the diagnosis of hypothyroidism, especially if systemic illness is not present. The definitive diagnosis must then rely on response to trial therapy with synthetic levothyroxine. Additional tests of thyroid gland function are warranted if the serum T<sub>4</sub> concentration is less than 0.8 to 1.0 μg/dl but clinical signs and physical examination findings are not strongly supportive of the disease and hypercholesterolemia is not present, if severe systemic illness is present and the potential for the euthyroid sick syndrome is high, or if medications known to decrease serum T<sub>4</sub> concentration are being administered.

Evaluation of a thyroid panel that includes serum  $T_4$ ,  $fT_4$ , TSH, and Tg autoantibody provides a more informative analysis of the pituitary-thyroid axis and thyroid gland function, can be used as the initial screening test for hypothyroidism, and should be used when serum  $T_4$  concentration alone

fails to establish the diagnosis. Low serum  $T_4$  and  $fT_4$ , and increased serum TSH concentrations in a dog with appropriate clinical signs and clinicopathologic abnormalities strongly support the diagnosis of hypothyroidism. Concurrent presence of Tg autoantibodies suggests lymphocytic thyroiditis as the underlying etiology.

Unfortunately, discordant test results are common. When this occurs, the appropriateness of clinical signs, clinicopathologic abnormalities, and clinician index of suspicion become the most important parameters when determining whether to treat the dog with levothyroxine. Serum fl'<sub>4</sub> concentration measured using ED or the 2-step RIA is the most accurate test of thyroid gland function and carries the highest priority, followed by serum T<sub>4</sub> concentration. Results of TSH concentration increase the likelihood of euthyroidism or hypothyroidism when TSH test results are consistent with results of serum fT4, but TSH test results should not be used as the sole indicator of hypothyroidism. Low serum fI4 and normal TSH test results occur in approximately 20% of dogs with hypothyroidism, and high TSH test results occur in euthyroid dogs with nonthyroidal illness and with medications such as phenobarbital and sulfonamides (see Tables 51-2 and 51-4). Normal serum fT<sub>4</sub> and high TSH may suggest early compensated hypothyroidism, but one has to wonder why clinical signs would develop when the serum fT4 concentration is normal. Positive Tg autoantibody findings merely suggest the possibility of lymphocytic thyroiditis; Tg autoantibody determination is not a thyroid function test. Positive results increase the suspicion for hypothyroidism if serum  $T_4$  or  $fT_4$  concentrations are low but have no bearing on the generation of clinical signs if serum T<sub>4</sub> and fT<sub>4</sub> concentrations are normal. When faced with discordant test results, the clinician must decide whether to initiate trial therapy with synthetic levothyroxine or repeat the tests sometime in the future—a decision that I usually base on the appropriateness of clinical signs and results of the fT<sub>4</sub> measured using ED or the 2-step RIA.

Admittedly, interpretation of serum T4, fT4, and TSH concentrations is not always simple. Because of the expense and frustration of working with tests that are not always reliable, many veterinarians and some clients prefer trial therapy as a diagnostic test. Trial therapy should be done only when thyroid hormone supplementation does not pose a risk to the patient. Response to trial therapy with sodium levothyroxine is nonspecific. A dog that has a positive response to therapy either has hypothyroidism or "thyroid-responsive disease." Because of its anabolic nature, thyroid supplementation can create an effect in a dog without thyroid dysfunction, especially regarding quality of the haircoat. Therefore, if a positive response to trial therapy is observed, thyroid supplementation should be gradually discontinued once clinical signs have resolved. If clinical signs recur, hypothyroidism is confirmed and the supplement should be reinitiated. If clinical signs do not recur, a thyroid-responsive disorder or a beneficial response to concurrent therapy (e.g., antibiotics, flea control) should be suspected.

# DIAGNOSIS IN A PREVIOUSLY TREATED DOG

Occasionally, a clinician wants to determine if a dog receiving thyroid hormone supplementation is in fact hypothyroid. The exogenous administration of thyroid hormone, either T4 or T3, will suppress pituitary TSH secretion and cause pituitary thyrotroph atrophy and subsequently thyroid gland atrophy in a healthy cuthyroid dog. Serum T<sub>4</sub>, fT<sub>4</sub>, and TSH concentrations are decreased or undetectable; the severity of the decrease is dependent on the severity of thyroid gland atrophy induced by the thyroid supplement. Serum T<sub>4</sub> and fT<sub>4</sub> results are often suggestive of hypothyroidism, even in a previously euthyroid dog, if testing is performed within a month of discontinuing treatment. Thyroid hormone supplementation must be discontinued and the pituitary-thyroid axis allowed to regain function before meaningful baseline serum thyroid hormone concentrations can be obtained. The time between discontinuation of thyroid hormone supplementation and acquisition of meaningful test results depends on the duration of treatment, the dose and frequency of administration of the thyroid hormone supplement, and individual variability. As a general rule, thyroid hormone supplements should be discontinued for a minimum of 4 weeks, preferably 6 to 8 weeks, before thyroid gland function is critically assessed.

#### DIAGNOSIS IN PUPPIES

An approach similar to that discussed in the previous section is used to diagnose congenital hypothyroidism. However, serum TSH concentrations are dependent on the etiology. TSH concentrations will be increased in dogs with primary dysfunction of the thyroid gland (e.g., iodine organification defect) and an intact hypothalamic-pituitary-thyroid gland axis. TSH concentrations will be within the normal range or undetectable in dogs with pituitary or hypothalamic dysfunction as the cause of the hypothyroidism.

#### Treatment

# THERAPY WITH SODIUM LEVOTHYROXINE (SYNTHETIC T4)

The initial treatment and monitoring recommendations are summarized in Box 51-5. Synthetic levothyroxine is the treatment of choice for hypothyroidism. Its administration orally should result in normal serum concentrations of T<sub>4</sub>, T<sub>3</sub>, and TSH, which attests to the fact that these products can be converted to the more metabolically active T<sub>3</sub> by peripheral tissues. A sodium levothyroxine product approved for use in dogs is recommended. Liquid and tablet formulations are effective. The initial dosage is 0.02 mg/kg body weight (0.1 mg/10 lb) with a maximum initial dose of 0.8 mg. Twice-daily administration is recommended initially unless the levothyroxine product has been specifically formulated for once-daily administration. Because of the variability in its absorption and metabolism, the dose and frequency may have to be adjusted before a satisfactory clinical response is



BOX 51-5

Recommendations for the Initial Treatment and Monitoring of Hypothyroidism in Dogs

#### **Initial Treatment**

Use a synthetic levothyroxine product approved for use in dogs.

Tablet and liquid formulations of levothyroxine are effective.

The initial dosage per administration should be 0.02~mg/kg (20  $\mu g/kg$ ) of body weight, with a maximum initial dose of 0.8~mg.

The initial frequency of administration is every 12 hours unless the levothyroxine product has been specifically formulated for once-daily administration.

#### **Initial Monitoring**

Response to treatment should be critically evaluated 4 to 8 weeks after initiating treatment.

Serum T<sub>4</sub> and TSH concentrations should be measured 4 to 6 hours after administration of levothyroxine.

Serum  $T_4$  should be in the reference range or increased. Serum TSH concentration should be in the reference range.

Measuring serum T<sub>4</sub> concentration immediately before levothyroxine administration (i.e., trough level) is optional but is recommended if levothyroxine is being given once a day.

The trough concentration of serum  $T_4$  should be in the reference range.

TSH, Thyroid-stimulating hormone.

observed; this variability is one reason for monitoring therapy in dogs.

# RESPONSE TO SODIUM LEVOTHYROXINE THERAPY

Thyroid hormone supplementation should be continued for a minimum of 4 weeks before critically evaluating the effectiveness of treatment. With appropriate therapy all clinical signs and clinicopathologic abnormalities associated with hypothyroidism are reversible. Improvement in mental alertness and activity usually occurs within the first week of treatment; this is an important early indicator that the diagnosis of hypothyroidism was correct. Although some hair regrowth usually occurs within the first month in dogs with endocrine alopecia, it may take several months for complete regrowth and a marked reduction in hyperpigmentation of the skin to occur. Initially, the haircoat may worsen as large amounts of hair in the telogen stage of the hair cycle are shed. Improvement in neurologic manifestations is usually evident within days of initiating treatment; complete resolution of neurologic signs is unpredictable and may take 4 to 8 weeks or longer of treatment before it occurs.



BOX 51-6

Potential Reasons for Poor Clinical Response to Treatment with Sodium Levothyroxine (Synthetic T<sub>4</sub>)

Client compliance problems
Use of inactivated or outdated product
Inappropriate levothyroxine dose
Inappropriate frequency of administration

Low tablet strength\*
Poor bioavailability (e.g., poor gastrotintestinal tract

absorption)
Inadequate time for clinical response to occur
Incorrect diagnosis of hypothyroidism

\* Tablet strength refers to actual amount of active drug in tablet, as opposed to the stated amount.

# FAILURE TO RESPOND TO SODIUM LEVOTHYROXINE THERAPY

Problems with levothyroxine therapy should be suspected if clinical improvement is not seen by 8 weeks after initiating therapy. An inappropriate diagnosis of hypothyroidism is the most obvious. Hyperadrenocorticism can be mistaken for hypothyroidism if other clinical signs (e.g., polyuria, polydipsia) commonly associated with hyperadrenocorticism are not present because of the suppressive effects of cortisol on serum thyroid hormone concentrations (see p. 738). Failure to recognize the impact of concurrent illness on thyroid hormone test results is another common reason for misdiagnosing hypothyroidism. Concurrent disease (e.g., allergic skin disease, flea hypersensitivity) is common in dogs with hypothyroidism and may affect the clinical impression of response to levothyroxine therapy if the disease is not recognized. Other possible reasons for a poor response to therapy are listed in Box 51-6. Whenever a dog shows a poor response to levothyroxine therapy, the history, physical examination findings, and diagnostic test results that prompted the initiation of levothyroxine therapy should be critically reevaluated and serum thyroid hormone concentrations measured.

#### THERAPEUTIC MONITORING

Therapeutic monitoring includes evaluation of the clinical response to levothyroxine treatment, measurement of serum  $T_4$  and TSH concentrations before or after levothyroxine administration, or both. These concentrations should be measured 4 weeks after initiating therapy, whenever signs of thyrotoxicosis develop, or in the event that there has been minimal or no response to therapy. Concentrations should also be measured 2 to 4 weeks after an adjustment in levothyroxine therapy in dogs showing a poor response to treatment.

Serum T<sub>4</sub> and TSH concentrations are typically evaluated 4 to 6 hours after the administration of levothyroxine in dogs receiving the medication twice daily and just before and 4 to

6 hours after administration in dogs receiving it once a day. Measurement of serum fT<sub>4</sub> can be done in lieu of measuring T<sub>4</sub> but is more expensive and probably does not offer additional information except in dogs with T<sub>4</sub> autoantibodies. The presence of thyroid hormone autoantibodies does not interfere with the physiologic actions of levothyroxine.

Ideally, the serum  $T_4$  concentration should be between 1.5 and 4.5 µg/dl when measured 4 to 6 hours after thyroid hormone administration and the TSH concentration should be in the reference range. Postdosing serum T<sub>4</sub> concentrations are frequently above the reference range. The finding of an increased postdosing serum T4 concentration is not an absolute indication to reduce the dose of levothyroxine, especially if there are no clinical signs of thyrotoxicosis. However, a reduction in the dose is recommended whenever serum T<sub>4</sub> concentrations exceed 6.0 μg/dl. Postdosing serum  $T_4$  concentrations may also be less than 1.5  $\mu$ g/dl. An increase in the dose or frequency of administration of levothyroxine is indicated if clinical manifestations of hypothyroidism persist, the serum TSH concentration remains increased, or both, but it is not necessarily indicated if the clinical response to treatment is good and the serum TSH concentration is in

the reference range. Postdosing serum  $T_4$  and TSH concentrations and recommendations for changes in therapy are given in Fig. 51-11.

#### **THYROTOXICOSIS**

Thyrotoxicosis may develop in dogs receiving excessive amounts of levothyroxine; in dogs in which the plasma halflife for levothyroxine is inherently prolonged, especially in those receiving levothyroxine twice daily; and in dogs with impaired metabolism of levothyroxine (e.g., concurrent renal or hepatic insufficiency). Rarely, thyrotoxicosis develops in a dog given minute amounts of levothyroxine. The reason for this marked sensitivity to the hormone is not known. Diagnosis of thyrotoxicosis is based primarily on presence of clinical signs, which include panting, nervousness, aggressive behavior, polyuria, polydipsia, polyphagia, and weight loss. Documenting increased serum T<sub>4</sub> and fT<sub>4</sub> and undetectable serum TSH concentrations supports the diagnosis. However, serum T4 and fT4 concentrations can occasionally be within the reference range in a dog with signs of thyrotoxicosis and are commonly increased in dogs with no signs of thyrotoxicosis. Adjustments in the dose or fre-

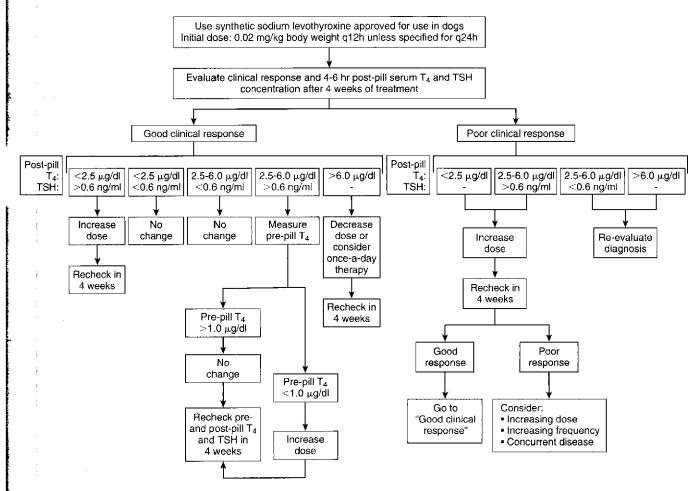


FIG 51-11
Initial therapeutic approach and monitoring recommendations for dogs with hypothyroidism.

quency of administration of levothyroxine, or both measures, are indicated if clinical signs of thyrotoxicosis develop in a dog receiving thyroid hormone supplements. Supplementation should be discontinued for a few days if clinical signs are severe. Signs of thyrotoxicosis should resolve within I to 3 days if they are due to the thyroid medication and the adjustment in treatment has been appropriate.

#### **Prognosis**

The prognosis for adult dogs with primary hypothyroidism that are receiving appropriate therapy is excellent. The prognosis for puppies with hypothyroidism (i.e., cretinism) is guarded and depends on the severity of skeletal and joint abnormalities at the time treatment is initiated. Although many of the clinical signs resolve with therapy, musculoskeletal problems, especially degenerative osteoarthritis, may develop owing to abnormal bone and joint development. The prognosis for dogs with secondary hypothyroidism caused by congenital malformation of the pituitary gland (i.e., pituitary dwarfism) is guarded to poor because of the multiple problems that develop in early life (see Chapter 49). The prognosis for dogs with acquired secondary hypothyroidism caused by suppression of pituitary function by medications (e.g., glucocorticoids) is excellent, although treatment with levothyroxine may be necessary if the medication can not be discontinued. The prognosis for dogs with acquired secondary hypothyroidism caused by destruction of the region by a space-occupying mass is grave.

#### HYPOTHYROIDISM IN CATS

#### Etiology

Iatrogenic hypothyroidism is the most common cause of hypothyroidism in cats and can result from bilateral thyroidectomy, radioactive iodine treatment, or an overdose of antithyroid drugs. Naturally acquired adult-onset primary hypothyroidism is rare. Congenital primary hypothyroidism causing disproportionate dwarfism is recognized more frequently in cats than adult-onset hypothyroidism. Reported causes of congenital hypothyroidism include a defect in thyroid hormone biosynthesis, most notably an iodine organification defect, and thyroid dysgenesis. Goiter is common in cats with defects in thyroid hormone biosynthesis because the hypothalamic-pituitary-thyroid gland axis remains intact. A suspected autosomal recessive inherited defect in iodine organification was documented in a family of Abyssinian cats with congenital hypothyroidism. Although rare, iodine deficiency may cause hypothyroidism in kittens fed a strict all-meat diet.

#### Clinical Signs

Clinical signs of feline hypothyroidism are listed in Box 51-7. The most common are lethargy, inappetence, obesity, and seborrhea sicca. Lethargy and inappetence may become severe. Additional dermatologic signs may include a dry, lusterless, unkempt haircoat; easily epilated hair; poor regrowth



BOX 51-7

Clinical Manifestations of Feline Hypothyroidism

#### **Adult-Onset Hypothyroidism**

Lethargy Inappetence

Obesity

Dermatologic

Seborrhea sicca

Dry, lusterless haircoat

Easily epilated hair

Poor regrowth of hair

Endocrine alopecia

Alopecia of pinnae Thickened skin

Myxedema of the face

Reproduction

Failure to cycle

Dystocia

Bradycardia

Mild hypothermia

#### Congenital Hypothyroidism

Disproportionate dwarfism

Failure to grow

Large head

Short, broad neck

Short limbs

Lethargy

Mental dullness

Constipation

Hypothermia

Bradycardia

Retention of kitten haircoat

Retention of deciduous teeth

of hair; and alopecia. Bradycardia and mild hypothermia may be additional findings on physical examination.

The clinical signs of congenital hypothyroidism are similar to those in dogs (see p. 729). Affected kittens typically appear normal at birth, but delayed growth usually becomes evident by 8 weeks of age. Disproportionate dwarfism develops over the ensuing months, with large heads; short, broad necks; and short limbs developing in affected kittens (Fig. 51-12). Additional findings include lethargy, mental dullness, constipation, hypothermia, bradycardia, and prolonged retention of deciduous teeth. The haircoat may consist mainly of an undercoat with primary guard hairs scattered thinly throughout.

#### Diagnosis

Establishing a diagnosis of hypothyroidism in the cat should be based on a combination of history, clinical signs, physical examination findings, results of routine blood and urine tests, and baseline serum  $T_4$  and  $fT_4$  concentrations. Measurement of serum TSH concentration using the canine TSH



#### FIG 51-12

A 1-year-old domestic long-haired cat with pituitary dwarfism. A comparably aged cat is also present to illustrate the small size of the pituitary dwarf. Note the square, chunky contour of the head and the dull facial expression of the cat—findings that are suggestive of cretinism (see Fig. 49-10, for comparison). The cat had concurrent growth hormone and thyroid hormone deficiency. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

assay should also be considered. Abnormalities identified on routine blood and urine tests include hypercholesterolemia and a mild nonregenerative anemia. Serum T<sub>4</sub> concentration is often used as the initial screening test of thyroid gland function. A normal serum T<sub>4</sub> concentration indicates that the cat is euthyroid. A low serum T<sub>4</sub> concentration in a cat that has undergone thyroidectomy or radioactive iodine treatment or in a kitten with disproportionate dwarfism supports the diagnosis of hypothyroidism. The effect of age should be considered when interpreting serum T<sub>4</sub> concentrations in kittens (see Table 51-2). Because naturally acquired primary hypothyroidism is rare and low serum T4 concentrations in adult cats is almost always caused by nonthyroidal illness (see Fig. 51-13) or some other nonthyroidal factor, the diagnosis of hypothyroidism should never be made solely on the basis of the serum T<sub>4</sub> concentration in an adult cat that has not been previously treated for hyperthyroidism. Documenting a low serum fT4 and high serum TSH concentration and failure of serum T<sub>4</sub> to increase following administration of rhTSH adds further evidence for the diagnosis of hypothyroidism. The definitive diagnosis relies on the cat's response to trial therapy with levothyroxine.

#### **Treatment**

Treatment of hypothyroidism in cats is similar to that used in dogs, which is described in detail on p. 741. Treatment with levothyroxine is indicated for cats with congenital and naturally acquired adult-onset hypothyroidism and for cats with iatrogenic hypothyroidism following treatment for hyperthyroidism that are symptomatic for the disease.

Asymptomatic cats with a low serum T<sub>4</sub> concentration following treatment for hyperthyroidism should not be treated until clinical signs become evident in the hope that additional time will allow atrophied or ectopic thyroid tissue to become functional.

Synthetic levothyroxine is recommended at an initial dosage of 0.05 or 0.1 mg once or twice daily. A minimum of 4 weeks should elapse before the cat's clinical response to treatment is critically assessed. Subsequent evaluations should include a history, physical examination, and measurement of serum T<sub>4</sub> concentration (see the discussion of therapeutic monitoring, p. 742). The goal of therapy is to eliminate the clinical signs of hypothyroidism and prevent signs of hyperthyroidism. This can usually be accomplished by maintaining the serum T<sub>4</sub> concentration between 1.0 and 2.5 µg/dl. The dose and frequency of levothyroxine administration should be adjusted accordingly to attain these goals. If the serum T<sub>4</sub> concentration is within the reference range after 4 to 8 weeks of treatment but there is minimal or no clinical response, the clinician should reassess the diagnosis.

#### **Prognosis**

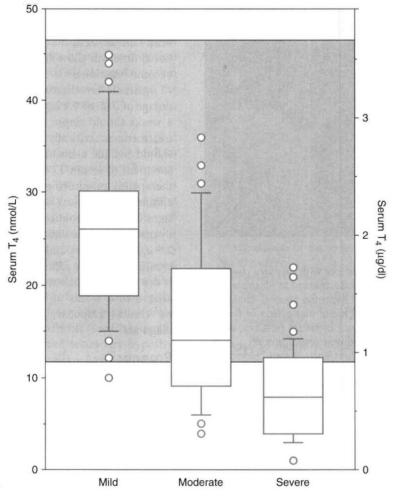
The prognosis for adult cats with hypothyroidism that are receiving appropriate therapy is excellent. The prognosis for kittens with congenital hypothyroidism is guarded and depends on the severity of the skeletal changes at the time treatment is initiated. Although many of the clinical signs resolve with therapy, musculoskeletal problems may persist or develop owing to abnormal bone and joint development.

#### HYPERTHYROIDISM IN CATS

#### Etiology

Hyperthyroidism is a multisystemic disorder resulting from the excessive production and secretion of  $T_4$  and  $T_3$  by the thyroid gland and is almost always a result of chronic intrinsic disease in one or both thyroid lobes. One or more usually small, discrete thyroid masses are palpable in the ventral region of the neck in most cats with hyperthyroidism. Multinodular adenomatous hyperplasia is the most common histologic finding. Less common are thyroid adenomas that cause the lobes to be enlarged and distorted; thyroid carcinoma accounts for fewer than 5% of clinical cases.

One or both thyroid lobes can be affected in thyrotoxic cats. Approximately 20% of hyperthyroid cats have involvement of a single thyroid lobe (Fig. 51-14). The nondiseased thyroid lobe is nonfunctioning and atrophied because of the suppressive effects of the hyperactive thyroid tissue on TSH secretion. More than 70% of hyperthyroid cats have involvement of both thyroid lobes (Fig. 51-15). Of these cats the thyroid lobes are symmetrically enlarged in 10% to 15% and asymmetrically enlarged in the remainder. Approximately 3% to 5% of thyrotoxic cats have hyperactive thyroid



**FIG 51-13**Box plots of serum total T<sub>4</sub> **(A)** and free T<sub>4</sub> **(B)** concentrations in 221 cats with nonthyroidal disease, grouped according to severity of illness. Of 221 cats with nonthyroidal illness 65 had mild disease, 83 had moderate disease, and 73 had severe disease. See Fig. 51-9 for explanation. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218:529, 2001.)

tissue in the anterior mediastinum, with or without a palpable mass in the neck (Fig. 51-16). Presumably, this tissue represents ectopic thyroid tissue. Functional thyroid carcinoma is the most likely diagnosis if more than two thyroid masses are present (see Fig. 51-16). Some of these cats initially have only one or two thyroid masses, emphasizing the importance of histologic evaluation of surgically removed tissue.

The pathogenesis of adenomatous hyperplastic changes of the thyroid gland remains unclear. It has been postulated that immunologic, infectious, nutritional, environmental, or genetic factors may interact to cause pathologic changes. Epidemiologic studies have identified consumption of commercial canned cat foods as a risk factor for development of hyperthyroidism, suggesting that a goitrogenic compound may be present in the diet. Excessive or deficient iodine

content, isoflavones from soybeans, and chemicals lining pop-top canned foods (specifically bisphenol A) that have migrated into the food during storage have been proposed as potential dietary and chemical goitrogens. Epidemiologic studies suggest that environmental factors such as use of kitty litter may be involved. Recent studies have identified overexpression of the c-ras oncogene in areas of nodular follicular hyperplasia in feline thyroid glands, suggesting that mutations in this oncogene may play a role in the etiopathogenesis of hyperthyroidism in cats (Merryman et al., 1999). In the normal cell activation of the ras protein leads to mitosis. Mutations of the ras oncogene produce mutated ras proteins that are not subject to the normal cellular feedback mechanisms that prevent uncontrolled mitosis. Altered expression of G proteins involved in the signal transduction pathway that stimulates growth and differentiation of thyroid

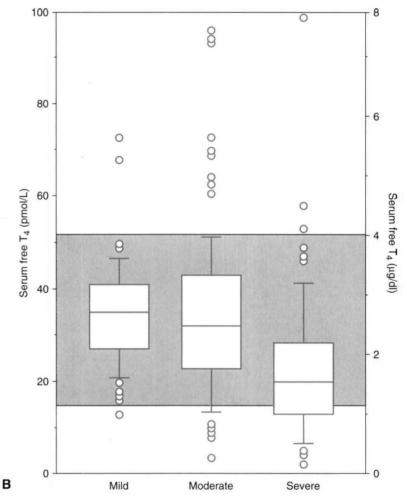


FIG 51-13, cont'd

cells has also been identified in adenomatous thyroid glands obtained from hyperthyroid cats (Ward et al., 2005). Decreased inhibitory G protein expression has been identified, a decrease that creates a relative increase in stimulatory G protein expression that may stimulate unregulated mitogenesis and thyroid hormone production in hyperthyroid cells. Further studies are necessary to clarify the significance of these findings and the relationships among abnormalities identified in thyroid cells from hyperthyroid cats, potential dietary or chemical goitrogens identified in canned cat foods, and the development of hyperthyroidism in cats.

#### **Clinical Features**

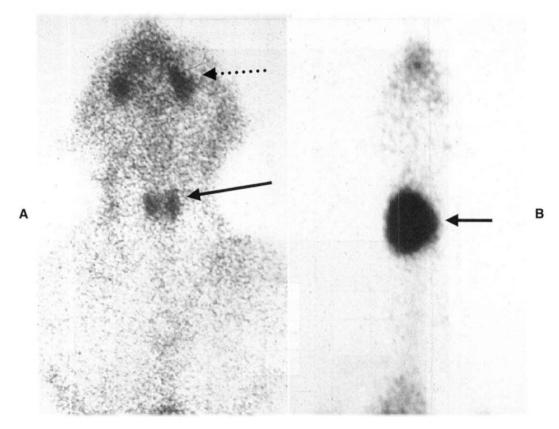
#### **SIGNALMENT**

Hyperthyroidism is the most common endocrine disease affecting cats older than 8 years. The average age at the time of initial presentation to the veterinarian is 13 years, with a range of 4 to 20 years. Fewer than 5% of cats with this disorder are younger than 8 years. There is no sex-related predisposition; domestic short-haired and long-haired cats are

the most frequently affected breeds. Siamese and Himalayans have a decreased risk for development of hyperthyroidism.

#### **CLINICAL SIGNS**

Clinical signs are a result of excessive secretion of thyroid hormone by the thyroid mass. Rarely, a client will seek veterinary care because of an observed mass in the ventrocervical region of the neck. The classic clinical signs of hyperthyroidism are weight loss (which may progress to cachexia), polyphagia, and restlessness or hyperactivity. Additional clinical signs include haircoat changes (patchy alopecia, matted hair, minimal or excessive grooming behavior), polyuria, polydipsia, vomiting, and diarrhea (Table 51-5). Some cats show aggressive behavior that resolves in response to successful treatment of the hyperthyroid state. In some cats lethargy, weakness, and anorexia are the dominant clinical features, in addition to weight loss. Because of the multisystemic effects of hyperthyroidism, the variable clinical signs, and its resemblance to many other diseases of the cat, hyperthyroidism should be suspected in any aged cat with medical problems.



#### FIG 51-14

**A,** Sodium pertechnetate scan of the head, neck, and proximal thorax of a healthy cat. Note that the uptake of pertechnetate (i.e., darkness) is comparable between the two thyroid lobes (solid arrow) and the salivary glands (broken arrow). **B,** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by unilateral disease affecting the right thyroid lobe (arrow). Note the difference in uptake of pertechnetate between the hyperfunctioning thyroid lobe and the salivary glands.



**TABLE 51-5** 

Clinical Signs and Physical Examination Findings in Cats with Hyperthyroidism

CLINICAL SIGNS	PHYSICAL EXAMINATION FINDINGS	
Weight loss*	Palpable thyroid*	
Polyphagia*	Thin*	
Unkempt haircoat, patchy alopecia*	Hyperactive, difficult to examine*	
Polyuria-polydipsia*	Tachycardia*	
Vomiting*	Hair loss, unkempt hair coat*	
Nervous, hyperactive	Small kidneys	
Diarrhea, bulky stools	Heart murmur	
Decreased appetite	Easily stressed	
Tremor	Dehydrated, cachectic appearance	
Weakness	Premature beats	
Dyspnea, panting	Gallop rhythm	
Decreased activity, lethargy	Aggressive	
Anorexia	Depressed, weak Ventral flexion of the neck	

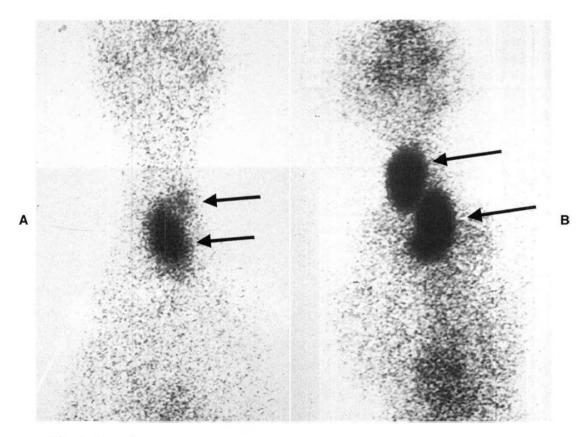
<sup>\*</sup> Common.

#### PHYSICAL EXAMINATION

Physical examination findings are listed in Table 51-5. A discrete thyroid mass is palpable in approximately 90% of cats with hyperthyroidism. However, the palpation of a cervical mass is not pathognomonic for hyperthyroidism. Some cats with palpable thyroid lobes are clinically normal, and some palpable cervical masses are not thyroid in origin. It is frequently difficult to accurately assess unilateral versus bilateral thyroid lobe involvement on the basis of palpation. Two distinct masses cannot always be appreciated on palpation, even if both lobes are large. Large thyroid masses may gravitate to the region of the thoracic inlet, which can interfere with their palpation. The thyroid mass may even descend into the anterior mediastinum. This should be suspected when a thyroid mass is not palpable in a hyperthyroid cat, although a small, nonpalpable mass is also possible.

#### **Clinical Pathology**

Results of a CBC are usually normal. The most common abnormalities are a mild increase in the PCV and mean corpuscular volume. Neutrophilia, lymphopenia, eosinopenia, or monocytopenia is identifed in less than 20% of hyperthyroid cats. Common serum biochemical abnormalities



# A, Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by bilateral, asymmetric disease affecting both thyroid lobes (arrows), with the right lobe more severely involved. This is the most common form of the disease. B, Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by bilateral, symmetric disease affecting both thyroid lobes (arrows). Hypocalcemia after bilateral thyroidectomy is a major concern.

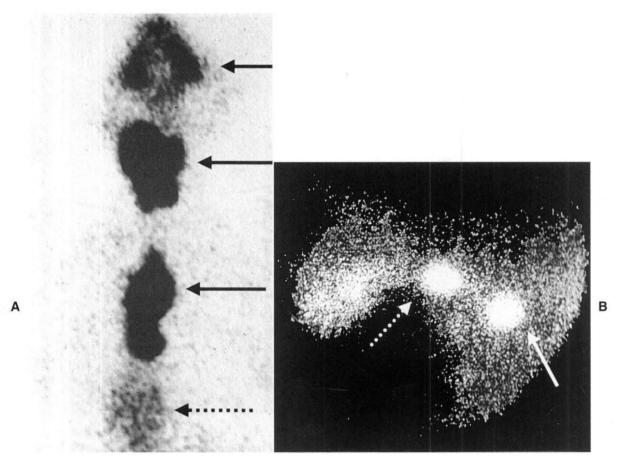
include an increase in serum activities of alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase; the increase is typically in the mild to moderate range (i.e., 100 to 400 IU/L). One or more of these liver enzymes are increased in approximately 90% of hyperthyroid cats. Additional evaluation of the liver should be considered if liver enzyme activities are greater than 500 IU/L. Increased serum urea nitrogen and creatinine concentrations are identified in approximately 25%, and hyperphosphatemia in 20%, of hyperthyroid cats at our clinic—findings that have important implications regarding treatment (see the discussion of renal insufficiency). Urine specific gravity ranges from 1.008 to greater than 1.050. Most hyperthyroid cats have urine specific gravities greater than 1.035. The remainder of the urinalysis is usually unremarkable unless concurrent diabetes mellitus or urinary tract infection exists.

# COMMON CONCURRENT PROBLEMS Thyrotoxic Cardiomyopathy

Hypertrophic and, less commonly, dilative thyrotoxic cardiomyopathy may develop in cats with hyperthyroidism. Cardiovascular abnormalities detectable during physical examination include tachycardia; a pounding heartbeat noted on palpation of the ventral thorax; and, less frequently, pulse deficits, gallop rhythms, cardiac murmur, and muffled heart sounds resulting from a pleural effusion. Electrocardiographic abnormalities include tachycardia; an increased Rwave amplitude in lead II; and, less commonly, a right bundle-branch block, a left anterior fascicular block, widened QRS complexes, and atrial and ventricular arrhythmias. Thoracic radiographs may reveal cardiomegaly, pulmonary edema, or a pleural effusion. Echocardiographic abnormalities identified in cats with hypertrophic thyrotoxic cardiomyopathy include left ventricular hypertrophy, thickening of the interventricular septum, left atrial and ventricular dilation, and myocardial hypercontractility. Those seen in cats with dilative thyrotoxic cardiomyopathy include subnormal myocardial contractility and marked ventricular dilation. Either form of cardiomyopathy may result in the development of congestive heart failure. Hypertrophic thyrotoxic cardiomyopathy is usually reversible once the hyperthyroid state is corrected, whereas dilative thyrotoxic cardiomyopathy is not.

#### Renal Insufficiency

Hyperthyroidism and renal insufficiency are common diseases of older cats and often occur concurrently. Identification



#### FIG 51-16

**A,** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by metastatic thyroid adenocarcinoma with multiple masses present in the head, neck, and anterior mediastinum (solid arrows). Heart (broken arrow). **B,** Sodium pertechnetate scan of the head, neck, and proximal thorax of a cat with hyperthyroidism caused by two hyperfunctioning masses: one located in the neck (broken arrow) and one in the anterior mediastinum (i.e., ectopic site) (solid arrow). Heart (broken arrow).

131 therapy is the treatment of choice for both forms of hyperthyroidism illustrated in this figure.

of small kidneys on physical examination, increased serum urea nitrogen and creatinine concentrations, and urine specific gravity between 1.008 and 1.020 should raise suspicion for concurrent renal insufficiency in a cat with hyperthyroidism. Unfortunately, hyperthyroidism increases glomerular filtration rate (GFR), renal blood flow, and renal tubular resorptive and secretory capabilities in normal and compromised kidneys. Renal perfusion and GFR may acutely decrease and azotemia or clinical signs of renal insufficiency become apparent or significantly worsen after treatment of the hyperthyroid state. It is not easy to determine what impact the hyperthyroid state is having on renal function in cats. The clinical and biochemical manifestations of renal failure may be masked in cats with both thyroid and renal disease in which renal perfusion is enhanced by the circulatory dynamics produced by hyperthyroidism. Thomas Graves, at the University of Illinois, has recently described a group of hyperthyroid cats with urine specific gravities greater than 1.040 that developed renal failure after treatment for hyperthyroidism, suggesting that urine specific gravity is a poor predictor of renal function in cats with hyperthyroidism. For these reasons cats with hyperthyroidism should initially be given reversible therapy (i.e., oral antithyroid drugs) until the impact of establishing euthyroidism on renal function can be determined (see p. 749).

#### **Urinary Tract Infections**

Urinary tract infections are relatively common in untreated hyperthyroid cats, with a reported prevalence of 12% to 22%. The most common bacterial isolate is *Escherichia coli*. Urine culture is indicated in hyperthyroid cats with lower urinary tract signs or presence of bacteriuria, pyuria, or both on urinalysis. Unfortunately, most hyperthyroid cats are asymptomatic for urinary tract infection, suggesting that urine culture should be a routine part of the complete diagnostic evaluation of cats with newly diagnosed hyperthyroidism.

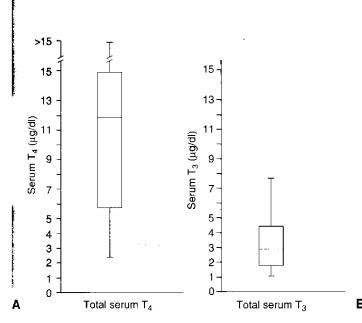


FIG 51-17

Mean and range of random total serum  $T_4$  (A) and total serum  $T_3$  (B) concentrations in hyperthyroid cats. Seventy-five percent of hyperthyroid cats have values within the box, and the balance is within the limitation bars above and below the box. Note that virtually all hyperthyroid cats have abnormal or borderline serum  $T_4$  concentrations, whereas serum  $T_3$  concentrations are less sensitive. The pink region represents the normal reference range.

#### **Systemic Hypertension**

Systemic hypertension is common in cats with hyperthyroidism and results from the effects of increased  $\beta$ -adrenergic activity on heart rate, myocardial contractility, systemic vasodilation, and activation of the renin-angiotensin-aldosterone system. Hypertension caused by hyperthyroidism is usually clinically silent. Retinal hemorrhages and retinal detachment are the most common clinical complications of systemic hypertension in hyperthyroid cats, but in general, ocular lesions are not commonly identified.

#### **Gastrointestinal Tract Disorders**

Gastrointestinal tract signs are common in cats with hyperthyroidism and include polyphagia, weight loss, anorexia, vomiting, diarrhea, increased frequency of defecation, and increased volume of feces. Intestinal hypermotility and malassimilation have been documented in some cats with hyperthyroidism and are responsible for producing some of the gastrointestinal tract signs. Inflammatory bowel disease is a common concurrent gastrointestinal tract disorder that should be considered in any hyperthyroid cat that has persistence of gastrointestinal signs after correction of the hyperthyroid state (see Chapter 33). Intestinal neoplasia, most notably lymphoma, is perhaps the most important differential diagnosis in cats seen because of polyphagia and weight loss. The abdomen should be carefully palpated in a search for thickening of the intestinal tract and mesenteric lymphadenopathy—findings that may be the only clues for



TABLE 51-6

Interpretation of Baseline Serum Thyroxine (T<sub>4</sub>)
Concentration in Cats with Suspected Hyperthyroidism

SERUM T4 CONCENTRATION	PROBABILITY OF HYPERTHYROIDISM	
>5.0 µg/dl	Very likely	
3.0-5.0 µg/dl	Possible	
2.5-3.0 µg/dl	Unknown	
2.0-2.5 µg/dl	Unlikely	
<2.0 µg/dl	Very unlikely*	

<sup>\*</sup> Assuming that a severe systemic illness is not present.

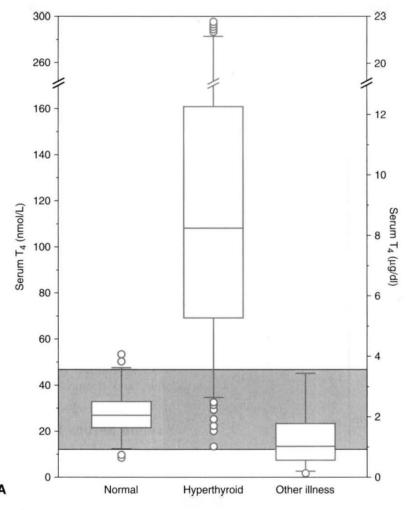
intestinal lymphoma. Abdominal ultrasonography may also provide clues to the possibility of lymphoma.

#### Diagnosis

The diagnosis of hyperthyroidism is based on identification of appropriate clinical signs, palpation of a thyroid nodule, and documentation of an increased serum  $T_4$  concentration.

#### Baseline Serum T<sub>4</sub> Concentration

Measurement of random baseline serum T<sub>4</sub> concentration has been extremely reliable in differentiating hyperthyroid cats from those without thyroid disease (Fig. 51-17). An abnormally high scrum T<sub>4</sub> concentration strongly supports the diagnosis of hyperthyroidism, especially if appropriate clinical signs are present, and a low serum T<sub>4</sub> concentration rules out hyperthyroidism, except in extremely uncommon situations when severe life-threatening nonthyroidal illness is present (Table 51-6). Serum T<sub>4</sub> concentrations that fall within the upper half of the normal range (i.e., 2.5 to 5.0 µg/ dl) create a diagnostic dilemma, especially if clinical signs are suggestive of hyperthyroidism and a nodule is palpable in the ventral region of the neck. This combination of findings is referred to as occult hyperthyroidism and is most commonly identified in cats in the early stages of hyperthyroidism. Serum T<sub>4</sub> concentrations are more likely to be influenced by nonthyroidal factors such as concurrent illness and are more likely to randomly fluctuate into the reference range in cats with mild hyperthyroidism, compared with cats with more advanced disease (Fig. 51-18; see also Fig. 51-13). The diagnosis of hyperthyroidism should not be excluded on the basis of one "normal" serum T<sub>4</sub> test result, especially in a cat with appropriate, albeit often mild, clinical signs and a palpable mass in the neck. Additional diagnostic factors to consider include measurement of serum free T<sub>4</sub> (fT<sub>4</sub>), the T<sub>3</sub> suppression test, sodium pertechnetate thyroid scan, or repetition of the serum T<sub>4</sub> test 3 to 6 months later. It is important to remember that the thyroid nodule may also be nonfunctional and the clinical signs may be the result of another disease (see Chapter 54).



Box plots of serum total T<sub>4</sub> **(A)** and free T<sub>4</sub> **(B)** concentrations in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. See Fig. 51-9 for explanation. (From Peterson ME et al: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease, *J Am Vet Med Assoc* 218:529, 2001.)

#### Serum Free T<sub>4</sub> Concentration

Measurement of serum fT<sub>4</sub> using equilibrium dialysis or the 2-step RIA (see p. 733) is the current recommendation of choice to confirm hyperthyroidism in a cat with nondiagnostic serum T<sub>4</sub> test results. Measurement of serum fT<sub>4</sub> is a more reliable means of assessing thyroid gland function than serum T<sub>4</sub> concentration, in part because nonthyroidal illness has less of a suppressive effect on serum fT<sub>4</sub> than T<sub>4</sub> (see Fig. 51-13) and serum  $fT_4$  is increased in many cats with occult hyperthyroidism and "normal" T4 test results. Because of cost, measurement of serum fT4 is often reserved for cats with suspected hyperthyroidism in which T<sub>4</sub> values are nondiagnostic. Concurrent illness may increase the serum fT4 concentration in cats, an increase that can exceed the reference range (see Fig. 51-18). For this reason serum fT4 concentration should always be interpreted in conjunction with a T<sub>4</sub> concentration measured from the same blood sample. An increased serum fT<sub>4</sub> concentration in conjunction with

high-normal or increased serum  $T_4$  concentration is supportive of hyperthyroidism. An increased serum  $fT_4$  concentration in conjunction with a low-normal or low serum  $T_4$  concentration is supportive of the euthyroid sick syndrome rather than hyperthyroidism.

#### T<sub>3</sub> Suppression Test

The  $T_3$  suppression test is used to distinguish euthyroid from mildly hyperthyroid cats in cases in which  $T_4$  and  $fT_4$  test results are nebulous. The  $T_3$  suppression test is based on the theory that oral administration of  $T_3$  will suppress pituitary TSH secretion in euthyroid cats, resulting in a decrease in circulating  $T_4$  (Fig. 51-19). In contrast, pituitary TSH secretion is already suppressed in cats with hyperthyroidism, oral administration of  $T_3$  will not cause further suppression, and serum  $T_4$  will not decrease following  $T_3$  administration. In this test 25  $\mu$ g of  $T_3$  (e.g., Cytomel, King Pharmaceuticals) is administered orally three times per day for seven treat-

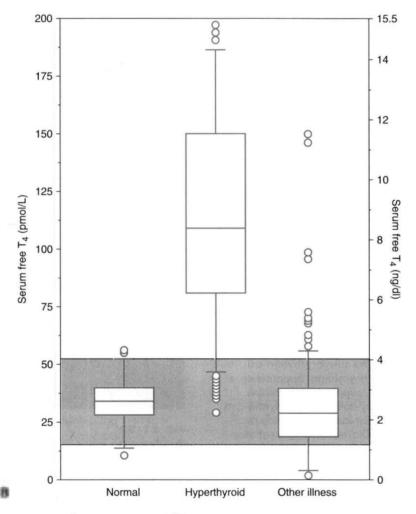


FIG 51-18, cont'd

ments and serum T<sub>4</sub> and T<sub>3</sub> concentration is determined before and 8 hours after the last T<sub>3</sub> administration. Normal cats consistently have postdosing serum T<sub>4</sub> concentrations of less than 1.5 ug/dl, whereas hyperthyroid cats have postdosing T<sub>4</sub> concentrations of greater than 2.0 µg/dl. Values of 1.5 to 2.0 µg/dl are nondiagnostic. The percentage decrease in the serum T<sub>4</sub> concentration is not as reliable a gauge as the absolute value, although suppression of more than 50% below the baseline value occurs in normal but not hyperthyroid cats. Serum T<sub>3</sub> concentrations are used to determine whether the client has successfully administered the thyroid medication to the cat. Serum T<sub>3</sub> concentration measured in the postpill blood sample should be increased compared with results obtained before initiating the test in all cats properly tested, regardless of the status of thyroid gland function.

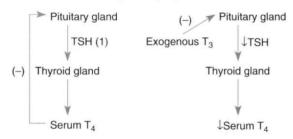
#### Radionuclide Thyroid Scanning

Radionuclide thyroid scanning identifies functional thyroid tissue and is used as a diagnostic test in cats with suspected occult hyperthyroidism; to identify ectopic thyroid tissue in cats with appropriate signs of hyperthyroidism and increased serum T<sub>4</sub> concentrations but no palpable thyroid

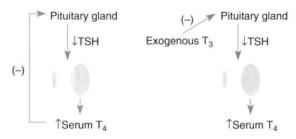
nodule in the neck; to identify sites of metastasis in cats with thyroid carcinoma; and to provide guidance for developing the best treatment plan, especially if thyroidectomy is being considered. Radioactive technetium 99m (pertechnetate) is used for routine imaging of the thyroid gland in cats. It has a short physical half-life (6 hours), is concentrated within functioning thyroid follicular cells, and reflects the trapping mechanism of the gland. Because antithyroid drugs do not affect the trapping mechanism of the thyroid pump, a pertechnetate scan can be done in cats being treated with antithyroid drugs. Salivary glands and the gastric mucosa also concentrate pertechnetate; it is excreted by the kidneys.

Scanning of the thyroid provides a picture of all functioning thyroid tissue and permits the delineation and localization of functioning as opposed to nonfunctioning areas of the thyroid. Fig. 51-14 shows the similarity between the size and shape of the thyroid lobes and similarity of radionuclide uptake by the thyroid and salivary glands in a normal cat. This 1:1 ratio of salivary gland to thyroid lobe uptake is the standard by which to judge the status of the thyroid. Findings in most hyperthyroid cats are markedly abnormal and usually easy to interpret (see Figs. 51-14 to 51-16).

#### Normal pituitary-thyroid axis



#### Hyperthyroidism



#### FIG 51-19

Effect of  $T_3$  supplementation on the pituitary-thyroid axis in healthy cats and cats with hyperthyroidism. Suppression of pituitary TSH secretion by the  $T_3$  supplement decreases serum  $T_4$  concentration in healthy cats. In hyperthyroid cats the serum TSH concentration is already suppressed; the  $T_3$  supplementation has no effect. The serum  $T_4$  concentration remains increased.

#### **Cervical Ultrasound**

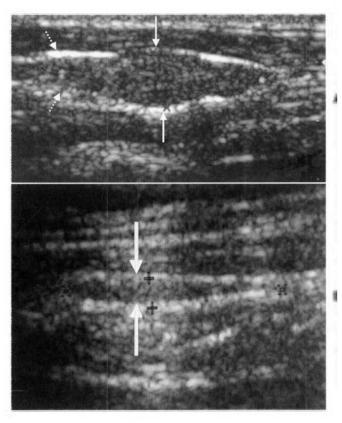
Ultrasonographic evaluation of the thyroid gland can be used to confirm the origin of the palpable cervical mass, differentiate unilateral versus bilateral thyroid lobe involvement, assess the size of the thyroid mass(es), and provide guidance for developing the best treatment plan (Fig. 51-20). Ultrasound does not provide information on the functional status of the thyroid mass and should not be used for establishing the diagnosis of hyperthyroidism. Rather, cervical ultrasound should be used as an adjunctive tool for locating cervical thyroid tissue.

#### **Treatment**

Hyperthyroidism in cats can be managed by thyroidectomy, oral antithyroid medications, or radioactive iodine (Table 51-7). All three modes of therapy are effective. Surgery and radioactive iodine treatments are used in the hope of providing a permanent cure for the disease; oral antithyroid drugs only control the hyperthyroidism and must be given daily to achieve and maintain their effect.

#### **Initial Treatment Recommendation**

Hyperthyroid cats should be treated initially with an oral antithyroid drug (i.e., methimazole) to reverse the hyperthyroid-induced metabolic and cardiac derangements, decrease the anesthetic risk associated with thyroidectomy, and assess the impact of treatment on renal function. Hyperthyroidism



#### FIG 51-20

**A,** Ultrasound image of the right thyroid lobe of a 13-year-old domestic short-haired cat with hyperthyroidism. A mass is in the midregion of the thyroid lobe (solid arrows). Normal appearing portion of thyroid lobe (broken arrows). **B,** Ultrasound image of the small (atrophied) normal left thyroid lobe (solid arrows). Left thyroid lobe (small arrows). Results of the ultrasound examination supported unilateral disease affecting the right thyroid lobe, which was confirmed with a sodium pertechnetate scan.

may mask renal insufficiency in some cats (see p. 749), and azotemia may develop or worsen and clinical signs of renal insufficiency may develop after treatment of the hyperthyroid state. Because it is not easy to determine what impact the hyperthyroid state is having on renal function, it is preferable to treat cats with reversible therapy (i.e., methimazole) until the impact of hyperthyroidism on renal function can be determined. If renal parameters remain static or improve after resolution of hyperthyroidism with methimazole, a more permanent treatment can be recommended. If significant azotemia or clinical signs of renal insufficiency develop during methimazole therapy, the treatment protocol for methimazole should be modified to attain the best possible control of both disorders and treatment for renal insufficiency should be instituted. Maintaining a mild hyperthyroid state may be necessary to improve renal perfusion and GFR and prevent the uremia of renal failure.

#### **Antithyroid Drugs**

Oral antithyroid drugs include methimazole, propylthiouracil, and carbimazole. Oral antithyroid drugs are inexpensive,



TABLE 51-7

Indications, Contraindications, and Disadvantages of the Three Modes of Therapy for Hyperthyroidism in Cats

THERAPY	INDICATIONS	RELATIVE CONTRAINDICATIONS	DISADVANTAGES
Methimazole, propylthiouracil, carbimazole	Long-term therapy for all forms of hyperthyroidism; initial therapy to stabilize cat's condition and assess renal function before thyroidectomy or radioactive iodine	None	Daily therapy required; no effect on growth of thyroid; mild adverse reactions common; severe reactions possible
Thyroidectomy	Unilateral lobe involvement; bilateral lobe involvement, asymmetrical sizes	Ectopic thyroid lobe; metastatic carcinoma; bilateral, symmetric, large lobes (high risk of hypocalcemia); severe systemic signs; cardiac arrhythmias or failure; renal insufficiency	Anesthetic risks; relapse of disease; postoperative complications, especially hypocalcemia
Radioactive iodine (131)	Therapy for all forms of hyperthyroidism; treatment of choice for ectopic thyroid lobe and thyroid carcinoma	Renal insufficiency	Limited availability; hospitalization time; potential for retreatment; hazardous to humans

readily available, relatively safe, and effective in the treatment of hyperthyroidism in cats. They inhibit the synthesis of thyroid hormone by blocking the incorporation of iodine into the tyrosyl groups in thyroglobulin and by preventing the coupling of these iodotyrosyl groups into T<sub>3</sub> and T<sub>4</sub>. Antithyroid drugs do not block the release of stored thyroid hormone into the circulation and do not have antitumor actions. Oral antithyroid drugs do not interfere with results of pertechnetate scanning or radioactive iodine therapy. Indications for oral antithyroid drugs include (1) test treatment to normalize serum T<sub>4</sub> concentrations and assess the effect of resolving hyperthyroidism on renal function, (2) initial treatment to alleviate or eliminate any medical problems associated with the syndrome before thyroidectomy is performed or before the hospitalization required for radioactive iodine treatment, and (3) long-term treatment of hyperthyroidism.

Methimazole (Tapazole; Eli Lilly & Co.) is currently the antithyroid drug of choice because the incidence of adverse reactions associated with its use is lower than that associated with the use of propylthiouracil (Table 51-8). Adverse reactions are less likely to occur when the dosage of methimazole is started low (typically at subtherapeutic dose initially) and gradually increased to effect. The recommended initial dose of methimazole is 2.5 mg administered orally twice a day for 2 weeks. If adverse reactions are not observed by the client, if the physical examination reveals no new problems, if results of a CBC and platelet count are within reference limits, if the serum creatinine and urea nitrogen concentrations have not increased, and if serum T4 concentration is greater than 2 µg/dl after 2 weeks of therapy, the dose is increased by 2.5 mg per day (i.e., 5 mg in the morning and 2.5 mg in the evening) twice daily and the same parameters evaluated 2 weeks later. The dosage should continue to be increased every 2 weeks by 2.5 mg/day increments until the serum  $T_4$  concentration is between 1 and 2  $\mu$ g/dl or adverse reactions develop. Serum  $T_4$  concentrations decline into the reference range within 2 weeks once the cat is receiving an effective dose of methimazole; clinical improvement is usually noted by clients within 2 to 4 weeks once good control of serum  $T_4$  concentration is achieved. Most cats respond to 5 to 7.5 mg of methimazole per day, and the drug is most effective when given twice a day. Attempts at decreasing the daily dosage, frequency of administration, or both can take place once clinical signs have resolved and a euthyroid state is attained, especially for cats receiving chronic methimazole treatment.

Rarely, cats are encountered that seem particularly resistant to methimazole, requiring as much as 20 mg/day. The most common cause for apparent resistance to methimazole is the inability of some clients to administer the drug to their cats. One alternative is to have a compounding pharmacy incorporate methimazole into tasty kitty treats. Another alternative is the topical application of methimazole to the pinna of the ear. Compounding veterinary pharmacies offer transdermal methimazole in a pluronic lecithin organogel (PLO) formulation. Creams can be made with methimazole at any concentration and are usually provided in 1-cc syringes that allow the client to place the appropriate dose on the fingertip and rub the cream into the pinna of the cat's ear. The client must wear gloves to avoid absorption of methimazole, should alternate ears, and should wipe away any residual cream 30 to 60 minutes after each administration. The dosage and frequency of administration is as discussed with oral methimazole treatment. The bioavailability of transdermal methimazole is more variable, the overall effectiveness



**TABLE 51-8** 

Abnormalities Associated with Methimazole Therapy in 262 Cats with Hyperthyroidism

		TIME TO DEVELOP (DAYS)	
CLINICAL SIGNS AND PATHOLOGY	PERCENTAGE OF CATS	MEAN	RANGE
Clinical Signs			
Anorexia	11	24	1 <i>-7</i> 8
Vomiting	11	22	<i>7</i> -60
Lethargy	9	24	1-60
Excoriations	2	21	6-40
Bleeding	2	31	1 <i>5-</i> 50
Clinical Pathology			
Positive Antinuclear antibody titer	22	91	10-870
Eosinophilia	11	57	12-490
Lymphocytosis	7	25	14-90
Leukopenia	5	23	10-41
Thrombocytopenia	3	37	14-90
Agranulocytosis	2	62	26-95
Hepatopathy	2	39	15-60

Adapted from Peterson ME, Kintzer PP, Hurvitz AI: Methimazole treatment of 262 cats with hyperthyroidism, J Vet Intern Med 2:150, 1988.

is not as good, and the prevalence of gastrointestinal adverse effects is lower, compared with oral methimazole. One important concern with using transdermal methimazole is the lack of regulation of compounding pharmacies; consistency between products created can vary considerably.

Adverse reactions to methimazole typically occur within the first 4 to 8 weeks of therapy (see Table 51-8). The cat should be examined every 2 weeks during the initial 3 months of methimazole treatment and a CBC, platelet count, assessment of kidney function, and serum T<sub>4</sub> concentration evaluated at each visit. After the initial 3 months of therapy a CBC, platelet count, serum biochemistry panel, and serum T<sub>4</sub> concentration should be evaluated every 3 to 6 months. Using the dosing protocol described above, lethargy, vomiting, and anorexia occur in fewer than 10% of cats; these mild adverse reactions are usually transient and often resolve despite continued administration of the drug. Mild methimazoleinduced hematologic changes occur in fewer than 10% of cats and include eosinophilia, lymphocytosis, and transient leukopenia. More worrisome but less common (fewer than 5% of cats) alterations include facial excoriations, thrombocytopenia (platelet counts less than 75,000/mm³), leukopenia (total white blood cell counts less than 2000/mm<sup>3</sup>), and immune-mediated hemolytic anemia. Apparent hepatic toxicity or injury occurs in fewer than 2% of cats receiving methimazole and is characterized by clinical signs of liver disease (i.e., lethargy, anorexia, vomiting), icterus, and increased serum alanine transaminase and alkaline phosphatase activities. Some cats test positive for antinuclear antibodies, but the importance of this finding is not known. Development of myasthenia gravis has also been reported with methimazole treatment. If any of these serious complications develop, methimazole treatment should be discontinued and supportive care given. Adverse reactions typically resolve within 1 week after methimazole treatment is discontinued. It is common for these potentially life-threatening adverse reactions to recur, regardless of the dose or type of antithyroid drug used; thus alternative therapy (i.e., surgery, radioactive iodine) is recommended.

Carbimazole (NeoMercazole; Amdipharm) is an antithyroid drug that is converted to methimazole in vivo; it is an effective alternative treatment if methimazole is not available. The dosage and frequency of administration are the same as those in oral methimazole treatment. Long-term, twice-daily schedules are effective in controlling hyperthyroidism. Adverse reactions are similar to those seen in cats receiving methimazole, but they occur less frequently. Cats being treated with carbimazole should be monitored in the same manner as that suggested for cats receiving methimazole.

#### Surgery

Thyroidectomy is an effective treatment but should always be considered an elective procedure. Surgery is not indicated if the risk of anesthesia in the cat is unacceptable, its renal function is questionable, the likelihood of postoperative hypocalcemia is great, ectopic thyroid tissue is present in the thorax, or thyroid carcinoma with metastasis is suspected. Treatment with methimazole for 1 to 2 months before thyroidectomy is recommended for reasons previously discussed. If possible, an ultrasound examination of the ventral neck or a radionuclide scan should be performed before surgery to identify the location of the abnormal thyroid tissue, differentiate unilateral from bilateral lobe involve-



BOX 51-8

# Complications of Thyroidectomy in Cats with Hyperthyroidism

Transient or permanent hypoparathyroidism causing hypocalcemia:

caicemia:

Restlessness

Irritability

Abnormal behavior

Muscle cramping, pain

Muscle tremors, especially of ears and face

Tetany

Convulsions

Laryngeal paralysis

Horner's syndrome

Hypothyroidism

Exacerbation of concurrent renal insufficiency

No amelioration of the hyperthyroidism

ment, and provide some insight into the probability of hypocalcemia developing postoperatively (see Fig. 51-15). Similar information can also be gained by direct visualization at the time of surgery.

Postoperative complications are listed in Box 51-8. The most worrisome is hypocalcemia. There is a direct correlation between the size of the thyroid lobes, the inability to visualize the external parathyroid glands, and the risk of hypocalcemia. Care must be taken to preserve at least one, preferably both, external parathyroid glands and their associated blood supply. A "subcapsular" thyroidectomy affords the best chance of retaining functional parathyroid glands. (See Suggested Readings for thyroidectomy procedures.) If all four parathyroid glands are inadvertently removed, the two external parathyroid glands should be removed from their respective thyroid lobes, minced, and placed within the muscle belly of one of the sternohyoideus muscles by bluntly dissecting parallel to the muscle fibers. Hypoparathyroidism usually resolves within a month of surgery if revascularization of the parathyroid autotransplant occurs.

Serum calcium concentration should be assessed at least once daily for 5 to 7 days if a bilateral thyroidectomy has been performed. Clinical signs of hypocalcemia typically develop within 72 hours of surgery, although signs may not develop for 7 to 10 days. These signs include lethargy, anorexia, reluctance to move, facial twitching (especially the ears), muscle tremors and cramping, tetany, and convulsions. If all four parathyroid glands are removed at surgery, appropriate calcium and vitamin D supplementation should be initiated once the cat has recovered from anesthesia (see p. 735). If at least one parathyroid gland has been spared, transient hypocalcemia may still develop and last for several days to weeks, probably as a result of disruption of blood flow to the parathyroid gland after surgical manipulation. In these cats oral vitamin D and calcium therapy should be initiated only if clinical signs develop or if hypocalcemia becomes severe (i.e., serum total or ionized calcium concentration less than 8 mg/dl and 0.8 mmol/L, respectively). A decline in the blood calcium concentration is not an absolute indication to begin therapy because the remaining parathyroid glands may respond before clinical signs or severe hypocalcemia develop.

The persistence of hypoparathyroidism is unpredictable. Parathyroid function may recover after days, weeks, or months of vitamin D and calcium supplementation. Whenever resolution of hypoparathyroidism is observed, it is assumed that reversible parathyroid damage occurred, accessory parathyroid tissue may be starting to compensate for glands damaged or removed at surgery, or the parathyroid autotransplant (if performed at surgery) has revascularized and become functional. It is also possible that calcium-regulating mechanisms are functioning in the absence of parathyroid hormone. Because it is difficult to predict the long-term requirement for vitamin D therapy in any cat, an attempt should be made to gradually wean all treated cats off medication while monitoring the serum calcium concentration. The tapering process should extend over a period of at least 12 to 16 weeks. The goal is to maintain the serum calcium concentration between 8.5 and 10.0 mg/dl. If hypocalcemia recurs, therapy with vitamin D and calcium must be reinstituted.

Hypothyroidism may develop in some cats after bilateral thyroidectomy. The clinical signs, diagnosis, and treatment are discussed on p. 744. The decision to initiate levothyroxine treatment should be based on the presence or absence of clinical signs, not on the serum  $T_4$  concentration, per se. Serum  $T_4$  concentrations commonly decrease after surgery, often to less than 0.5  $\mu g/dl$ , but thyroid function returns in most cats before clinical signs become apparent. Thyroid hormone supplementation should be initiated in cats that develop clinical signs in conjunction with a low serum  $T_4$  concentration. Because thyroid replacement therapy may not be needed long term in some of these cats, thyroid replacement therapy should be tapered slowly and then discontinued after 1 to 3 months to determine the continued need for treatment.

If clinical signs of hyperthyroidism persist despite thyroidectomy, the serum T4 concentration should be measured. If the serum T<sub>4</sub> concentration is low-normal or low (i.e., <2.0 µg/dl), another disorder should be suspected. If the serum T<sub>4</sub> concentration is high-normal or high (i.e., >4.0 µg/dl), ectopic abnormal thyroid tissue, metastatic thyroid carcinoma, or, if unilateral thyroidectomy was performed, abnormal tissue in the remaining thyroid lobe should be suspected. Ectopic thyroid tissue would most likely be in the mediastinum, cranial to the heart (see Fig. 51-16). Thyroid scanning is recommended to identify ectopic or metastatic thyroid tissue. Alternatively, oral methimazole or radioactive iodine therapy can be considered. Clinical signs of hyperthyroidism may also recur months to years after thyroidectomy. The serum T4 concentration should be monitored once or twice a year in all cats successfully treated with surgery.

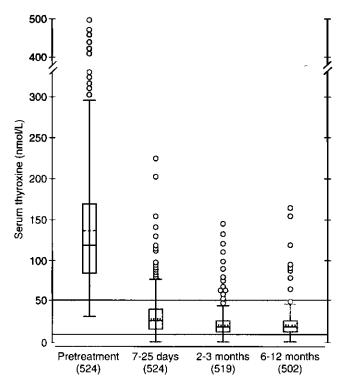


FIG 51-21
Box plots of serum thyroxine (T₄) concentrations in 524 cats before and at various times after administration of radioiodine for treatment of hyperthyroidism. The shaded area indicates the reference range for serum T₄ concentration. Please see Fig. 51-9 for the key. (From Peterson ME et al: Radioiodine treatment of 524 cats with hyperthyroidism, J Am Vet Med Assoc 207:1422, 1995.)

#### Radioactive Iodine

If available, radioactive iodine is the treatment of choice for hyperthyroidism because of the very low morbidity and mortality and very high success rate associated with the treatment (Fig. 51-21). Hypoparathyroidism is not a concern with radioactive iodine treatment, is effective in cats with hyperfunctioning ectopic thyroid tissue, and is the only option offering the potential for a cure in cats with metastatic or nonresectable thyroid carcinoma. Treatment with methimazole for 1 to 2 months before radioactive iodine treatment is recommended for reasons previously discussed. Prior or current treatment with methimazole does not alter the efficacy of radioactive iodine treatment.

Iodine 131 (<sup>131</sup>I) has a half-life of 8 days and is the radionuclide of choice for treating hyperthyroidism. <sup>131</sup>I administered intravenously or subcutaneously is concentrated within the thyroid, and the emitted radiation destroys surrounding functioning follicular cells while causing minimal radiation damage to contiguous structures. At doses of 3 to 5 mCi of <sup>131</sup>I, the thyroid cells killed are those that are functioning. Atrophied normal thyroid cells receive a relatively small dose of radiation and are usually able to return to function, thereby preventing hypothyroidism in most cats. Depending on the dose administered, more than 80% of treated cats become euthyroid within 3 months—most within 1 week and more than 95% of treated cats are euthyroid at 6 months. In one study by Peterson et al. (1995), clinical signs and laboratory data consistent with hypothyroidism developed in approximately 2% of 254 131 I-treated cats, 2% to 4% required a second 131I treatment, and hyperthyroidism recurred in 2% within 1 to 6 years of treatment. Chun et al. (2002) found no correlation between pretreatment serum T<sub>4</sub> concentration or thyroid to salivary gland ratios and resolution of hyperthyroidism after treatment with radioactive iodine. The most common complication following radioactive iodine treatment is hypothyroidism, which typically develops in cats with large, diffusely affected thyroid lobes receiving large doses of <sup>131</sup>I. The duration of hospitalization following 131I administration varies depending on state regulations and the dosage of 131 I administered. In our hospital the average cat is treated with 3 to 5 mCi of <sup>131</sup>I and requires 4 to 6 days of hospitalization after therapy until the radioactivity of the cat and its excretions reach an acceptable level.

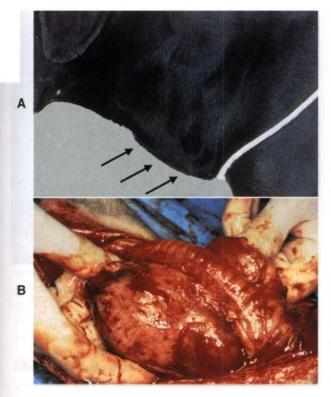
#### **Prognosis**

The prognosis is excellent for most cats with hyperthyroidism, assuming concurrent disease can be managed and thyroid carcinoma is not the etiology. Surgery and <sup>131</sup>I therapy have the potential for cure, although hyperthyroidism may recur months to years (or not at all) after thyroidectomy or <sup>131</sup>I treatment. Hyperthyroid cats with adenomatous hyperplasia or adenoma can potentially be treated with methimazole for years, assuming adverse reactions related to the medication are avoided. In a recent retrospective study cats with concurrent renal disease had significantly shorter survival times than cats with normal renal function and the survival time in cats treated with methimazole alone (median 2 years; interquartile range 1 to 3.9 years) was significantly shorter than cats treated with <sup>134</sup>I alone (4.0 years; 3.0 to 4.8 years) or methimazole followed by <sup>131</sup>I (5.3 years; 2.2 to 6.5 years; Milner et al., 2006).

#### CANINE THYROID NEOPLASIA

#### Etiology

Thyroid adenomas are usually small, nonfunctional masses that do not cause clinical signs and are usually found incidentally at necropsy. Exceptions are thyroid adenomas that are functional and cause hyperthyroidism or are unexpectedly identified during ultrasound examination of the ventral neck. Thyroid carcinomas are more commonly identified antemortem because of their large size, presence of clinical signs that can be recognized by clients, and ease of palpation by veterinarians. One or both thyroid lobes may be involved, and ectopic thyroid tissue located in the anterior mediastinum and base of the heart occasionally may become neoplastic. Thyroid carcinomas frequently infiltrate into surrounding structures such as the esophagus, trachea, and cervical musculature. Regional and distant metastasis to the



#### FIG 51-22

**A,** A 13-year-old male Labrador Retriever was presented to the veterinarian because the client noticed a mass in the neck (arrows). The mass was a thyroid adenocarcinoma. **B,** Thyroid adenocarcinoma in an 11-year-old mixed-breed dog. Clinical signs included dysphagia, coughing, and a visible mass in the ventral region of the neck.

retropharyngeal and cervical lymph nodes and lungs is common. Metastasis to other locations such as the liver, kidney, bone, and brain is also possible.

Most dogs with thyroid tumors are euthyroid or hypothyroid; approximately 10% of dogs have functional thyroid tumors that secrete excess thyroid hormone, causing hyperthyroidism. Clinical signs of hyperthyroidism may predominate in these dogs. Hyperthyroidism may be caused by functional thyroid adenomas and carcinomas. Adenomatous hyperplasia is the most common cause of hyperthyroidism in cats but has not been described in dogs.

#### **Clinical Features**

Thyroid tumors occur in middle-aged to older dogs, with an average age of 10 years. There is no sex-related predilection. Although any breed can be affected, Boxers, Beagles, and Golden Retrievers may be at an increased risk.

Dogs with nonfunctional thyroid tumors are usually brought to veterinarians because the client has seen or felt a mass in the ventral region of the dog's neck (Fig. 51-22). Clinical signs may develop as a result of the mass compressing on adjacent structures (e.g., dyspnea, dysphagia) or as a result of metastasis (e.g., exercise intolerance, weight loss; Box 51-9). Clinical signs of hypothyroidism may develop



#### BOX 51-9

#### Clinical Signs Caused by Thyroid Neoplasia in Dogs

# Nonfunctional Swelling or mass in neck Dyspnea Cough Lethargy Dysphagia Regurgitation Anorexia Weight loss Horner's syndrome Change in bark

#### Functional (Hyperthyroid)

Facial edema

Swelling or mass in neck
Polyphagia and weight loss
Hyperactivity
Polyuria and polydipsia
Panting
Change in behavior
Aggression

with large invasive tumors that destroy both thyroid lobes. Clinical signs of hyperthyroidism occur in approximately 10% of dogs with thyroid tumors and are similar to those seen in hyperthyroid cats (see p. 748).

Most thyroid tumors are firm, asymmetric, lobulated, and nonpainful masses located close to the typical thyroid region in the neck. The mass is usually well embedded in surrounding tissue and not freely movable. Additional physical examination findings may include dyspnea, cough, cachexia, lethargy, Horner's syndrome, and dehydration. A dry, lusterless haircoat is common, but alopecia is rare. Mandibular or cervical lymph nodes (or both) may be enlarged as a result of tumor spread or lymphatic obstruction. Dogs with functional thyroid tumors may be restless, thin, and panting, and auscultation of the heart frequently reveals tachycardia. Surprisingly, many dogs are found to be remarkably healthy on physical examination.

CBC, serum biochemistry panel, and urinalysis findings usually do not help establish the diagnosis. A mild normocytic, normochromic, nonregenerative anemia, hypercholesterolemia, and hypertriglyceridemia causing lipemia may be present in dogs with concurrent hypothyroidism. A mild increase in the blood urea nitrogen concentration and liver enzyme activities has been identified in less than 35% of dogs; however, the latter changes were not found to be indicative of hepatic metastasis. Hypercalcemia has also been noted in a few dogs.

Baseline serum  $T_4$  and  $fT_4$  concentrations are increased and serum TSH is undetectable in dogs with a functional thyroid tumor causing hyperthyroidism. However, most canine thyroid tumors are nonfunctional, and most of these

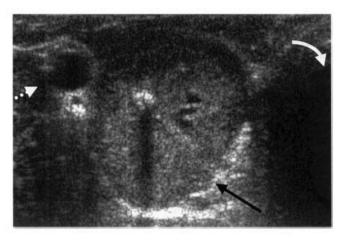


FIG 51-23

Ultrasound image of a mass in the region of the right thyroid lobe (straight arrow), the carotid artery (broken arrow), and the trachea (curved arrow) in an 11-year-old female spayed Labrador mix. A small region of mineralization causing a shadowing effect is evident within the mass. The mass was an unexpected finding during a routine physical examination. Thyroid adenocarcinoma was the histopathologic diagnosis after surgical removal of the mass.

dogs are found to be euthyroid when serum thyroid hormone concentrations are evaluated. Approximately 30% of dogs with thyroid tumors have serum  $T_4$  and  $fT_4$  concentrations below the reference range and suggestive of hypothyroidism resulting from destruction of normal thyroid tissue by the tumor. However, interpretation of low serum thyroid hormone concentrations must be done with caution and consideration of the suppressive effects of nonthyroidal illness on thyroid function (see p. 737).

Cervical ultrasonography will confirm the presence of a mass, regardless of its size and location; can distinguish between cavitary, cystic, and solid tumors; can identify the presence and severity of local tumor invasion; can identify the presence and location of metastatic sites in the cervical region; and improve the likelihood that representative tissue for cytologic or histologic evaluation is obtained during fineneedle aspiration or percutaneous biopsy of the mass (Fig. 51-23). Because metastasis to the lungs and base of the heart is common with thyroid carcinoma, thoracic radiographs should always be included in the diagnostic evaluation of dogs with a suspected thyroid mass. Cervical radiographs may identify a small mass that was suspected but not definitively identified on physical examination, may show the severity of the displacement of adjacent structures, and may identify local invasion of the mass into the larynx and trachea. Abdominal ultrasonography can be used to identify abdominal (most notably hepatic) metastatic lesions. Computed tomographic and magnetic resonance imaging can define the extent of tumor invasion into surrounding structures, identify distant metastasis to the lymph nodes and lung, and identify ectopic thyroid tissue in the mediastinum (Fig. 51-24)—information that is valuable if surgery or megavoltage irradiation is being considered.



FIG 51-24

Magnetic resonance image of a right-sided thyroid mass (solid arrow) adjacent to the trachea (broken arrow) in a 10-year-old male castrated Golden Retriever that was presented for a swelling in the neck. The histopathologic diagnosis was thyroid C-cell carcinoma with vascular invasion. The affected region of the neck was treated with radiation after thyroidectomy.

Thyroid scans using sodium pertechnetate can be used to confirm that a cervical mass is thyroid in origin; assess the degree of regional tissue invasion; and identify unusual areas of uptake in the head, neck, and thorax suggestive of metastatic sites. Most thyroid carcinomas demonstrate heterogenous uptake of pertechnetate, irregular gland shape, and evidence of regional tissue invasion. If the malignancy, especially a distant site of metastasis, does not trap iodine effectively, the scintigraphic study will fail to identify the site. Failure to identify distant metastatic sites with scintigraphy does not mean that distant metastasis does not exist. The amount of radionuclide uptake by the thyroid tumor is not a reliable indicator of its functional status (i.e., euthyroid, hypothyroid, or hyperthyroid) or the benign versus malignant nature of the tumor. Thoracic radiographs are more sensitive than a thyroid scan for identifying pulmonary metastasis.

#### Diagnosis

For a definitive diagnosis to be rendered, a biopsy specimen must be obtained from the tumor and evaluated histologically. Unfortunately, canine thyroid tumors are highly vascular, and it is common for hemorrhage to occur after biopsy. Fine-needle aspiration using a 21- or 23-gauge needle and cytologic examination of the mass are recommended initially to confirm that the mass is of thyroid origin. Contamination of the aspirate with blood is common, and differentiation between adenoma and carcinoma is difficult. Large-bore needle biopsy, surgical exploration, or ultrasound-guided biopsy is often required to confirm the diagnosis. Ultrasonography identifies solid areas of the mass to

biopsy and large blood vessels to be avoided. This procedure is preferred if the findings yielded by needle aspiration are inconclusive.

#### **Treatment**

Treatment options for thyroid tumors in dogs include surgery, chemotherapy, megavoltage irradiation, radioactive iodine, and antithyroid drugs. The therapeutic approach is based, in part, on the size and invasiveness of the tumor and the presence of regional and distant metastasis. The functional status of the thyroid tumor does not dramatically alter the treatment approach. All thyroid tumors in dogs should be considered malignant until proved otherwise. Treatment is warranted even for large, locally invasive tumors. Many dogs with large invasive tumors appear more comfortable and have the potential for increased longevity after treatment. In addition, local control of the tumor may halt or reduce metastatic spread, and the presence of metastatic spread may not ultimately affect outcome. Local control of the thyroid carcinoma is of primary importance in managing this disease.

#### **SURGERY**

Surgical excision of thyroid adenomas and small, well-encapsulated, movable thyroid carcinomas is likely to be curative. Surgical removal of a fixed, invasive thyroid carcinoma, regardless of size, carries a guarded to poor prognosis for complete excision of the tumor. Megavoltage irradiation is the treatment of choice for these tumors. Chemotherapy is indicated if distant metastasis is identified. Surgical debulking of fixed, invasive tumors is indicated to relieve tumorinduced problems such as dysphagia or dyspnea and allow more time for other therapies to work. Surgical debulking may also be considered after megavoltage irradiation or chemotherapy has caused the size of large invasive tumors to shrink. Aggressive attempts at surgical removal, especially of bilateral tumors, threaten the integrity of recurrent laryngeal nerves, parathyroid glands, and normal thyroid tissue. It is important to monitor serum calcium concentrations before and for 7 to 10 days after surgery if there is any chance that the parathyroid glands have been excised or damaged. Vitamin D and calcium therapy should be initiated if any evidence of hypoparathyroidism is found (see p. 735). Serum T<sub>4</sub>, fT<sub>4</sub>, and TSH concentrations should be monitored 2 to 3 weeks after surgery and, depending on clinical signs, replacement therapy implemented accordingly (see p. 741). (See Slatter [2003] and Fossum [2007] for information on surgical techniques for the thyroparathyroid complex.)

#### **MEGAVOLTAGE IRRADIATION**

Megavoltage irradiation is the treatment of choice for locally advanced thyroid carcinoma. Megavoltage irradiation can be used alone or in conjunction with surgery or chemotherapy. There is a slow regression rate of thyroid carcinoma after radiation therapy in dogs. In one study involving 25 dogs with unresectable differentiated thyroid carcinoma and no evidence of metastasis, the time to attain maximum reduc-

tion in tumor size ranged from 8 to 22 months after megavoltage irradiation (Theon et al., 2000). Progression-free survival rates (defined as the time between completion of irradiation and detection of measurable local tumor recurrence or death from causes unrelated to tumor progression) were 80% at 1 year and 72% at 3 years with a mean progression-free survival time of 55 months in the 25 dogs. Acute radiation reactions to megavoltage irradiation include esophageal, tracheal, or laryngeal mucositis causing dysphagia, cough, and hoarseness. These reactions tend to be mild and self-limiting. Chronic radiation reactions include skin fibrosis, permanent alopecia, chronic tracheitis causing a dry cough, and hypothyroidism.

#### CHEMOTHERAPY

Chemotherapy is indicated when total surgical removal or destruction with megavoltage irradiation is not successful, if distant metastatic lesions have been identified, and if the size of the primary tumor is such that local invasion or metastasis is likely, even though it cannot be identified with diagnostic tests. Whenever the thyroid mass exceeds approximately 4 cm in diameter, the probability of metastasis becomes extremely high. Doxorubicin given at a dosage of 30 mg/m<sup>2</sup> body surface area intravenously every 3 to 6 weeks is the historic treatment of choice. The response of canine thyroid tumors to doxorubicin is variable. In most dogs doxorubicin prevents further growth of the tumor and may cause the tumor to shrink, but total remission is uncommon. Combination chemotherapy with 5-fluorouracil, cyclophosphamide, and/or vincristine may enhance the effectiveness of doxorubicin. Cisplatin or carboplatin should be considered in dogs that fail to respond to or have recurrence of disease with doxorubicin therapy. The response to cisplatin has been reported to be similar to the response to doxorubicin, although several cisplatin-treated dogs were previously treated with doxorubicin (Fineman et al., 1998). (See Chapters 77 and 78 for a discussion of the use of these chemotherapeutic agents.)

#### RADIOACTIVE IODINE (1311)

Recent retrospective studies suggest that 131 therapy will prolong survival times when used as sole therapy or in combination with surgery for the treatment of thyroid tumors in dogs. Worth et al. (2005) reported a median survival time of 30 months for dogs treated with radioiodine alone, 34 months when radioiodine was combined with surgery, and 3 months for dogs that did not receive treatment. Turrell et al. (2006) reported a median survival time of 839 days for dogs with local or regional tumors (i.e., stage II and III disease) and 366 days for dogs with metastasis. Tumor site (cervical versus ectopic), age, body weight, treatment protocol (131 alone or with surgery), and serum T<sub>4</sub> concentration were not significantly associated with survival time. Iodine 131 therapy is useful for any thyroid tumor tissue that can accumulate organic iodine, including metastatic sites. Kinetic studies to evaluate the ability of the tumor to trap iodine should be conducted before considering radioactive iodine treatment. Large doses of <sup>131</sup>I (i.e., 30 to 150 mCi) are typically administered intravenously or subcutaneously to treat canine thyroid tumors. Potential adverse reactions include esophagitis, tracheitis, and bone marrow suppression.

#### **ORAL ANTITHYROID DRUGS**

Oral antithyroid drugs are used as palliative therapy to control the clinical signs of hyperthyroidism in dogs with functional thyroid tumors. Oral antithyroid drugs are not used as a primary treatment because they are not cytotoxic. The therapeutic approach is similar to that used in hyperthyroid cats (see p. 754), beginning with 2.5 mg of methimazole administered twice a day, with subsequent increases in the dosage and frequency of administration as needed to control clinical signs and maintain the serum T<sub>4</sub> concentration within the reference range.

#### **Prognosis**

The prognosis for thyroid adenomas is excellent after surgical removal. The prognosis is guarded to good for dogs that undergo surgical resection of small, well-encapsulated carcinomas. Unfortunately, most dogs have relatively large thyroid masses, which have frequently invaded surrounding tissues or metastasized at the time of diagnosis. In these dogs aggressive therapy using multiple treatments can alleviate the clinical signs and in some cases dramatically reduce the tumor burden. The long-term prognosis, however, remains guarded to poor, with survival times typically ranging from 6 to 24 months, depending on the aggressiveness of treatment.

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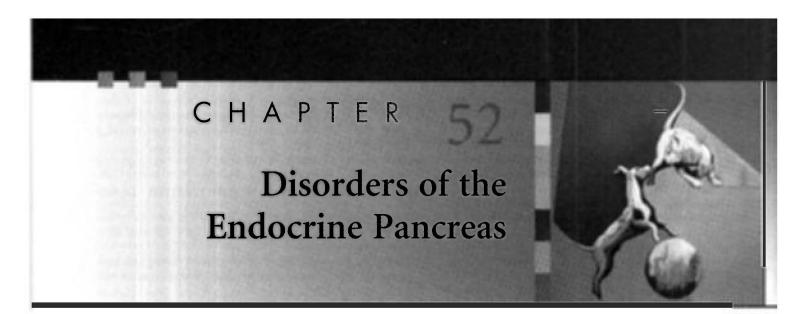
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#### CHAPTER OUTLINE

HYPERGLYCEMIA HYPOGLYCEMIA DIABETES MELLITUS IN DOGS

Signalment

History

Physical Examination

Overview of Insulin Preparations

Storage and Dilution of Insulin

Initial Insulin Recommendations for Diabetic Dogs

Diet

Exercise

Identification and Control of Concurrent Problems

Protocol for Identifying Initial Insulin Requirements

History and Physical Examination

Single Blood Glucose Determination

Serum Fructosamine Concentration

Urine Glucose Monitoring

Serial Blood Glucose Curves

Insulin Therapy During Surgery

Complications of Insulin Therapy

Chronic Complications of Diabetes Mellitus

#### DIABETES MELLITUS IN CATS

Signalment

History

Physical Examination

Initial Insulin Recommendations for Diabetic Cats

Diet

Identification and Control of Concurrent Problems

Oral Hypoglycemic Drugs

Identifying Initial Insulin Requirements

Insulin Therapy During Surgery

Complications of Insulin Therapy

Chronic Complications of Diabetes Mellitus

#### DIABETIC KETOACIDOSIS

Fluid Therapy

Insulin Therapy

Concurrent Illness

Complications of Therapy for Diabetic Ketoacidosis

#### INSULIN-SECRETING B-CELL NEOPLASIA

Signalment

Clinical Signs

Physical Examination

Clinical Pathology

Overview of Treatment

Perioperative Management of Dogs Undergoing Surgery

Postoperative Complications

Medical Treatment for Chronic Hypoglycemia

GASTRIN-SECRETING NEOPLASIA

#### **HYPERGLYCEMIA**

#### **Etiology**

Hyperglycemia is present if the blood glucose concentration is greater than 130 mg/dl, although clinical signs of hyperglycemia do not develop until the renal tubular threshold for the resorption of glucose is exceeded. In dogs this typically occurs whenever the blood glucose concentration exceeds 180 to 220 mg/dl. The threshold for glucose resorption appears to be more variable in cats, ranging from 200 to 280 mg/dl. Glycosuria causes an osmotic diuresis, which in turn causes polyuria and polydipsia, the hallmark clinical signs of severe hyperglycemia (greater than 180 mg/dl in dogs and greater than 200 to 280 mg/dl in cats). The most common cause of hyperglycemia and glycosuria is diabetes mellitus. Severe hyperglycemia without glycosuria also occurs commonly in cats with stress-induced hyperglycemia, presumably resulting from the secretion of catecholamines and possibly lactate. Transient glycosuria (typically less than 1% on urine glucose test strips) may occur in some cats with severe or prolonged stress-induced hyperglycemia.

#### **Clinical Features**

Hyperglycemia of between 130 and 180 mg/dl (possibly as high as 280 mg/dl in cats) is clinically silent and is often an unsuspected finding encountered during blood testing for another reason. If a dog or cat with mild hyperglycemia (less than 180 mg/dl) and no glycosuria is seen because of poly-



#### Causes of Hyperglycemia in Dogs and Cats

Diabetes mellitus\*

Stress, aggression, excitement, nervousness, fright\*

Postprandial (within 2 hours of consuming diets containing monosaccharides, disaccharides, propylene glycol, corn

syrup)

Hyperadrenocorticism\*

Acromegaly (cat)

Diestrus (bitch)

Pheochromocytoma (dog)

**Pancreatitis** 

Exocrine pancreatic neoplasia

Renal insufficiency

Head trauma

Drug therapy\*

Glucocorticoids

Ciococornicola

**Progestins** 

Megestrol acetate

Dextrose-containing fluids\*

Parenteral nutrition solutions\*

uria and polydipsia, a disorder other than overt diabetes mellitus should be suspected. Mild hyperglycemia can occur in some dogs and cats up to 2 hours after consumption of diets containing increased quantities of monosaccharides and disaccharides, corn syrup, or propylene glycol; during intravenous (IV) administration of total parenteral nutrition fluids; in stressed, agitated, or excitable cats and dogs; in animals in the early stages of diabetes mellitus; and in animals with disorders and drugs causing insulin resistance (Box 52-1). A diagnostic evaluation for disorders causing insulin resistance is indicated if mild hyperglycemia is found to persist in a fasted, unstressed dog or cat, especially if the blood glucose concentration is increasing over time (see p. 783).

#### HYPOGLYCEMIA

#### Etiology

Hypoglycemia is present if the blood glucose concentration is less than 60 mg/dl. It typically results from the excessive use of glucose by normal cells (e.g., during periods of hyperinsulinism) or neoplastic cells, impaired hepatic gluconeogenesis and glycogenolysis (e.g., portal shunt, hepatic cirrhosis), a deficiency in diabetogenic hormones (e.g., hypocortisolism), an inadequate dietary intake of glucose and other substrates required for hepatic gluconeogenesis (e.g., anorexia in the neonate or toy breeds), or a combination of these mechanisms (e.g., sepsis; Box 52-2). Iatrogenic hypoglycemia is a common problem resulting from overzealous insulin administration in diabetic dogs and cats.



#### Causes of Hypoglycemia in Dogs and Cats

β-Cell tumor (insulinoma)\*

Extrapancreatic neoplasia

Hepatocellular carcinoma, hepatoma\*

Leiomyosarcoma, leiomyoma\*

Hemangiosarcoma

Carcinoma (mammary, salivary, pulmonary)

Leukemia

Plasmacytoma

Melanoma

Hepatic insufficiency\*

Portal caval shunts

Chronic fibrosis, cirrhosis

Sepsis\*

Severe canine babesiosis

Septic peritonitis

Hypoadrenocorticism\*

Trypoddrenocomcism

ldiopathic hypoglycemia\*

Neonatal hypoglycemia

Juvenile hypoglycemia (especially toy breeds)

Hunting dog hypoglycemia

Exocrine pancreatic neoplasia

**Pancreatitis** 

Renal failure

Hypopituitarism

Severe polycythemia

Hepatic enzyme deficiencies

Von Gierke's disease (type I glycogen storage disease)

Cori's disease (type III glycogen storage disease)

Prolonged starvation

Prolonged sample storage\*

latrogenic\*

Insulin therapy

Sulfonylurea therapy

Ethylene glycol ingestion

Artifact\*

Portable blood glucose monitoring devices

Laboratory error

Prolonged storage of blood before separation of serum or plasma causes the glucose concentration to decrease at a rate of approximately 7 mg/dl/h. Glycolysis by red and white blood cells becomes even more apparent in dogs and cats with erythrocytosis, leukocytosis, or sepsis. Therefore whole blood obtained for the measurement of the glucose concentration should be separated soon after collection (within 30 minutes), and the serum or plasma should be refrigerated or frozen until the assay is performed to minimize artifactual lowering of the blood glucose concentration. Glucose determinations from separated and refrigerated plasma or serum are reliable for as long as 48 hours after the separation and refrigeration of the specimen. Alternatively, plasma can be collected in sodium fluoride tubes. Unfortunately, hemolysis is common in blood collected in sodium fluoride-treated

<sup>\*</sup>Common cause.

<sup>\*</sup> Common cause.

tubes, which can result in slight decrements in glucose values owing to methodologic problems in laboratory determinations. Blood glucose values determined by many portable home blood glucose—monitoring devices are typically lower than actual glucose values determined by bench-top methodologies, and this may result in an incorrect diagnosis of hypoglycemia. Finally, a laboratory error may also result in an incorrect value. It is wise to confirm hypoglycemia by determining the blood glucose concentration from a second blood sample and using bench-top methodology before embarking on a search for the cause of hypoglycemia.

#### **Clinical Features**

Clinical signs of hypoglycemia usually develop when the blood glucose concentration is less than 45 mg/dl, although this can be quite variable. The development of clinical signs depends on the severity and duration (acute versus chronic) of hypoglycemia and the rate of decline in the blood glucose concentration. Clinical signs are a result of neuroglycopenia and hypoglycemia-induced stimulation of the sympathoadrenal nervous system. Neuroglycopenic signs include seizures; weakness; collapse; ataxia; and, less commonly, lethargy, blindness, bizarre behavior, and coma. Signs of increased secretion of catecholamines include restlessness, nervousness, hunger, and muscle fasciculations.

Depending on the cause, the signs of hypoglycemia may be persistent or intermittent. The hallmark clinical sign of hypoglycemia (i.e., seizures) tends to be intermittent, regardless of the cause. Dogs and cats usually recover from hypoglycemic seizures within 30 seconds to 5 minutes as a result of activation of counterregulatory mechanisms (e.g., secretion of glucagon and catecholamines) that block the effects of insulin, stimulate hepatic glucose secretion, and promote an increase in the blood glucose concentration.

#### **Diagnostic Approach**

Hypoglycemia should always be confirmed before beginning diagnostic studies to identify the cause. Careful evaluation of the animal's history, physical examination findings, and results of routine blood tests (i.e., complete blood count [CBC], serum biochemistry panel, urinalysis) usually provides clues to the underlying cause. Hypoglycemia in the puppy or kitten is usually caused by idiopathic hypoglycemia, starvation, liver insufficiency (i.e., portal shunt), or sepsis. In young adult dogs or cats hypoglycemia is usually caused by liver insufficiency, hypoadrenocorticism, or sepsis. In older dogs or cats liver insufficiency,  $\beta$ -cell neoplasia, extrapancreatic neoplasia, hypoadrenocorticism, and sepsis are the most common causes.

Hypoglycemia tends to be mild (greater than 45 mg/dl) and is often an incidental finding in dogs and cats with hypoadrenocorticism or liver insufficiency. Additional clinical pathologic alterations are usually present (e.g., hyponatremia and hyperkalemia in animals with Addison's disease or increased alanine aminotransferase [ALT] activity, hypocholesterolemia, hypoalbuminemia, and a low blood urea nitrogen [BUN] concentration in animals with liver

insufficiency). An adrenocorticotropic hormone (ACTH) stimulation test or liver function test (i.e., preprandial and postprandial bile acids) may be required to confirm the diagnosis. Severe hypoglycemia (less than 40 mg/dl) may develop in neonates and juvenile kittens and puppies (especially toy breeds) and in animals with sepsis, β-cell neoplasia, and extrapancreatic neoplasia, most notably hepatic adenocarcinoma and leiomyosarcoma. Sepsis is readily identified on the basis of physical examination findings and abnormal CBC findings, such as a neutrophilic leukocytosis (typically greater than 30,000/µl), a shift toward immaturity, and signs of toxicity. Extrapancreatic neoplasia can usually be identified on the basis of the physical examination, abdominal or thoracic radiography, and abdominal ultrasonography findings. Dogs with  $\beta$ -cell neoplasia typically have normal physical examination findings and no abnormalities other than hypoglycemia identified on routine blood and urine tests. Measurement of baseline serum insulin concentration when the blood glucose is less than 60 mg/dl (preferably less than 50 mg/dl) is necessary to confirm the diagnosis of a β-cell tumor.

#### **Treatment**

Whenever possible, therapy should always be directed at eliminating the underlying cause of the hypoglycemia. If the disorder cannot be eliminated and the clinical signs of hypoglycemia persist, long-term symptomatic therapy designed to increase the blood glucose concentration may be necessary to minimize clinical signs (see Box 52-12). Such therapy is usually required for animals with metastatic  $\beta$ -cell or extrapancreatic neoplasia.

Symptomatic therapy for animals with severe hypoglycemia of acute onset relies on the administration of glucose (Box 52-3). If the dog or cat is having a hypoglycemic seizure at home, the client should rub a sugar mixture on the pet's buccal mucosa. Most animals respond within 1 to 2 minutes. Clients should be instructed never to place fingers in, or pour the sugar solution down, the pet's mouth. Once the dog or cat is sternal and cognizant of its surroundings, it should be fed a small meal and brought to the veterinarian.

If collapse, seizures, or coma develops in the hospital, a blood sample should be obtained to measure the glucose concentration and other variables before reversing the signs with the IV administration of 50% dextrose. Dextrose should be administered in small amounts slowly rather than in large boluses rapidly. This is especially important in dogs with suspected  $\beta$ -cell neoplasia in which aggressive glucose administration can result in severe hypoglycemia after excessive insulin secretion by the tumor in response to the glucose. Commonly, 2 to 15 ml of 50% dextrose is required to alleviate the signs. Dogs and cats with hypoglycemia usually respond to glucose administration within 2 minutes. Recurrence of hypoglycemia is dependent on the ability to correct the underlying etiology.

Occasionally, a dog or cat with severe central nervous system signs (e.g., blindness, coma) does not respond to initial glucose therapy. Irreversible cerebral lesions may result from prolonged severe hypoglycemia and the resultant



BOX 52-3

Medical Therapy for Acute Hypoglycemic Scizures

#### Seizures at Home

Step 1. Rub or pour sugar solution on pet's gums.

Step 2. Once pet is sternal, feed a small meal.

Step 3. Call the veterinarian.

#### Seizures in Hospital

Step 1. Administer 1 to 5 ml of 50% dextrose IV *slowly* over 10 minutes.

Step 2. Once animal is sternal, feed a small meal.

Step 3. Initiate chronic medical therapy if necessary (see Box 52-12).

#### Intractable Seizures in Hospital

Step 1. Administer 2.5% to 5% dextrose in water intravenously at 1.5 to 2 times maintenance fluid rate.

Step 2. Add 0.5 to 1 mg of dexamethasone/kg to IV fluids and administer over 6 hours; repeat every 12 to 24 hours, as necessary.

Step 3. Administer IV glucagon USP (Eli Lilly Co.) by constant-rate infusion at an initial dosage of 5 to 10 ng/kg/min (see p. 805).

Step 4. If preceding steps fail, anesthetize animal for 4 to 8 hours while continuing previously described therapy.

IV, Intravenous.

cerebral hypoxia. The prognosis in these animals is guarded to poor. Therapy is directed at providing a continuous supply of glucose by administering a 2.5% to 5% solution intravenously or increasing hepatic gluconeogenesis with a constant rate infusion of glucagons (see p. 805). Seizure activity is controlled with diazepam or a stronger anticonvulsant medication. Glucocorticoids and mannitol may be necessary to combat cerebral edema.

#### DIABETES MELLITUS IN DOGS

#### **Etiology**

Virtually all dogs with diabetes have insulin-dependent diabetes mellitus (IDDM) at the time of diagnosis. IDDM is characterized by hypoinsulinemia, essentially no increase in the endogenous serum insulin concentration after the administration of an insulin secretagogue (e.g., glucose or glucagon) at any time after the diagnosis of the disease, failure to establish glycemic control in response to diet or treatment with oral hypoglycemic drugs (or both), and an absolute need for exogenous insulin to maintain glycemic control. The cause of diabetes mellitus has been poorly characterized in dogs but is undoubtedly multifactorial. A genetic predisposition, infection, insulin-antagonistic diseases and drugs, obesity, immune-mediated insulitis, and pancreatitis have been identified as inciting factors. The end result is a loss of  $\beta$ -cell function, hypoinsulinemia, impaired transport

of circulating glucose into most cells, and accelerated hepatic gluconeogenesis and glycogenolysis. The subsequent development of hyperglycemia and glycosuria causes polyuria, polydipsia, polyphagia, and weight loss. Ketoacidosis develops as the production of ketone bodies increases to compensate for the underutilization of blood glucose (see p. 794). Loss of  $\beta$ -cell function is irreversible in dogs with IDDM, and lifelong insulin therapy is mandatory to maintain glycemic control of the diabetic state.

Unlike cats, dogs very rarely have a transient or reversible form of diabetes mellitus. The most common scenario for transient diabetes mellitus in dogs is correction of insulin antagonism after ovariohysterectomy in a bitch in diestrus. Progesterone stimulates secretion of growth hormone in the bitch. Ovariohysterectomy removes the source of progesterone, plasma growth hormone concentration declines, and insulin antagonism resolves. If an adequate population of functional β cells are still present in the pancreas, hyperglycemia may resolve without the need for insulin treatment. These dogs have a significant reduction in  $\beta$ -cell numbers (i.e., subclinical diabetes) compared with healthy dogs, before the development of hyperglycemia during diestrus, and are prone to redevelopment of hyperglycemia and diabetes mellitus if insulin antagonism recurs for any reason after ovariohysterectomy. Although uncommon, a similar situation can occur in dogs with subclinical diabetes treated with insulin-antagonistic drugs (e.g., glucocorticoids) or in the very early stages of an insulin-antagonistic disorder (e.g., hyperadrenocorticism). Failure to quickly correct the insulin antagonism will result in IDDM and the lifelong requirement for insulin treatment to control the hyperglycemia.

A honeymoon period occurs in some dogs with newly diagnosed IDDM. It is characterized by excellent glycemic control in response to small doses of insulin (less than 0.2 U/kg/injection), presumably because of the presence of residual  $\beta$ -cell function. However, glycemic control becomes more difficult and insulin doses usually increase within 3 to 6 months of starting treatment as residual functioning  $\beta$  cells are destroyed and endogenous insulin secretion declines. It is very uncommon for non–insulin-dependent diabetes mellitus (NIDDM) to be recognized clinically in dogs, despite the documentation of obesity-induced carbohydrate intolerance in dogs and the identification of residual  $\beta$ -cell function in some diabetic dogs.

#### **Clinical Features**

#### **SIGNALMENT**

Most dogs are 4 to 14 years old at the time diabetes mellitus is diagnosed, with a peak prevalence at 7 to 9 years of age. Juvenile-onset diabetes occurs in dogs younger than 1 year of age and is uncommon. Female dogs are affected about twice as frequently as male dogs. Genetic predispositions to the development of diabetes are suspected in some breeds on the basis of familial associations and pedigree analysis (Table 52-1).



**TABLE 52-1** 

Breeds Recognized to Have High and Low Risk for Developing Diabetes Mellitus Based on Analysis of the Veterinary Medical Database (VMDB) from 1970 to 1993.\*

BREEDS WITH HIGH RISK	ODDS RATIO	BREEDS WITH LOW RISK	ODDS RATIO
Australian Terrier	9.39	German Shepherd Dog <sup>†</sup>	0.18
Standard Schnauzer	5.85	Collie	0.21
Miniature Schnauzer <sup>†</sup>	5.10	Shetland Sheepdog	0.21
Bichon Frise	3.03	Golden Retriever <sup>†</sup>	0.28
Spitz	2.90	Cocker Spaniel	0.35
Fox Terrier	2.68	Australian Shepherd	0.44
Miniature Poodle <sup>†</sup>	2.49	Labrador Retriever	0.45
Samoyed <sup>†</sup>	2.42	Doberman Pinscher	0.49
Cairn Terrier	2.26	Boston Terrier	0.51
Keeshond	2.23	Rottweiler	0.51
Maltese	1.79	Basset Hound	0.56
Toy Poodle <sup>†</sup>	1.76	English Setter	0.60
Lhasa Apso	1.54	Beagle	0.64
Yorkshire Terrier	1.44	Irish Setter	0.67
Pug <sup>†</sup>	The state of the s	English Springer Spaniel	0.69
		American Pit Bull Terrier	

From Guptill L et al: Is canine diabetes on the increase? In *Recent advances in clinical management of diabetes mellitus*, lams Company, Dayton, Ohio, 1999, p. 24. Mixed-breed dogs were used as the reference group (Odds Ratio 1.00) for comparison with other breeds.

\* The VMDB comprises medical records of 24 veterinary schools in the United States and Canada. VMDB case records analyzed included those from first hospital visits of 6078 dogs with a diagnosis of diabetes mellitus and 5,922 randomly selected dogs with first hospital visits for any diagnosis other than diabetes mellitus seen at the same veterinary schools in the same year. Only breeds with more than 25 cases of diabetes mellitus are included.

<sup>1</sup>Breeds also identified with significant high or low risk for developing diabetes in a study by Hess RS et al: Breed distribution of dogs with diabetes mellitus admitted to a tertiary care facility, J Am Vet Med Assoc 216:1414, 2000.

#### **HISTORY**

The history in virtually all diabetic dogs includes polydipsia, polyuria, polyphagia, and weight loss. Polyuria and polydipsia do not develop until hyperglycemia results in glycosuria. Occasionally, a client brings in a dog because of sudden blindness caused by cataract formation (Fig. 52-1). The typical clinical signs of diabetes were either unnoticed or considered irrelevant by the client. If the clinical signs associated with uncomplicated diabetes are not observed by the client and impaired vision caused by cataracts does not develop, a diabetic dog is at risk for the development of systemic signs of illness as progressive ketonemia and metabolic acidosis develop. The time sequence from the onset of initial clinical signs to the development of diabetic ketoacidosis (DKA) is unpredictable, ranging from days to weeks.

### PHYSICAL EXAMINATION

Physical examination findings depend on the presence and severity of DKA, on the duration of diabetes before its diagnosis, and on the nature of any other concurrent disorder. The nonketotic diabetic dog has no classic physical examination findings. Many diabetic dogs are obese but are otherwise in good physical condition. Dogs with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., pancreatic exocrine insufficiency) is present. The haircoat may be sparse; the hairs may be dry,



Bilateral cataracts causing blindness in a diabetic dog. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

brittle and lusterless; and scales from hyperkeratosis may be present. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Lenticular changes consistent with cataract formation are common. Additional abnormalities may be identified if DKA is present (see p. 796).

## **Diagnosis**

The diagnosis of diabetes mellitus is based on three findings: appropriate clinical signs, persistent fasting hyperglycemia, and glycosuria. Measurement of the blood glucose concentration using a portable blood glucose–monitoring device and testing for the presence of glycosuria using urine reagent test strips (e.g., KetoDiastix; Ames Division, Miles Laboratories) provides rapid confirmation of diabetes mellitus. Concurrent documentation of ketonuria establishes a diagnosis of diabetic ketosis (DK), and documentation of metabolic acidosis establishes a diagnosis of DKA.

It is important to document both persistent hyperglycemia and glycosuria to establish a diagnosis of diabetes mellitus because hyperglycemia differentiates diabetes mellitus from primary renal glycosuria and glycosuria differentiates diabetes mellitus from other causes of hyperglycemia (see Box 52-1), most notably epinephrine-induced stress hyperglycemia that may develop around the time of blood sampling. Stress-induced hyperglycemia is a common problem in cats and occasionally occurs in dogs, especially those that are very excited, hyperactive, or aggressive. The reader is referred to p. 792 for more information on stress-induced hyperglycemia.

A thorough evaluation of the dog's overall health is recommended once the diagnosis of diabetes mellitus has been established to identify any disease that may be causing or contributing to the carbohydrate intolerance (e.g., hyperadrenocorticism), that may result from the carbohydrate intolerance (e.g., bacterial cystitis), or that may mandate a modification of therapy (e.g., pancreatitis). The minimum laboratory evaluation should include a CBC, serum biochemistry panel, measurement of serum pancreatic lipase immunoreactivity, and urinalysis with bacterial culture. Serum progesterone concentration should be determined if diabetes mellitus is diagnosed in an intact bitch, regardless of her cycling history. If available, abdominal ultrasound is indicated to assess for pancreatitis, adrenomegaly, pyometritis in an intact bitch, and abnormalities affecting the liver and urinary tract (e.g., changes consistent with pyelonephritis or cystitis). Measurement of baseline serum insulin concentration or an insulin response test is not routinely done. Additional tests may be warranted after obtaining the history, performing the physical examination, or identifying ketoacidosis. Potential clinical pathologic abnormalities are listed in Box 52-4.

#### **Treatment**

The primary goal of therapy is elimination of client-observed clinical signs of diabetes. Persistence of clinical signs and development of chronic complications (Box 52-5) are directly correlated with the severity and duration of hyperglycemia. In the diabetic dog establishing control of hyperglycemia can be accomplished with insulin, diet, exercise, prevention or control of concurrent insulin antagonistic diseases, and discontinuation of medications that cause insulin resistance. The veterinarian must also guard against development of hypoglycemia, a serious and potentially fatal com-



BOX 52-4

Clinicopathologic Abnormalities Commonly Found in Dogs and Cats with Uncomplicated Diabetes Mellitus

#### **Complete Blood Count**

Typically normal

Neutrophilic leukocytosis, toxic neutrophils if pancreatitis or infection present

#### **Biochemistry Panel**

Hyperglycemia

Hypercholesterolemia

Hypertriglyceridemia (lipemia)

Increased alanine aminotransferase activity (typically <500 IU/L)

Increased alkaline phosphatase activity (typically <500 IU/L)

#### Urinalysis

Urine specific gravity typically >1.025 Glycosuria Variable ketonuria Proteinuria Bacteriuria

#### **Ancillary Tests**

Serum lipase normal or increased if pancreatitis present Serum amylase normal or increased if pancreatitis present Serum trypsinlike immunoreactivity (TLI)

Low if pancreatic exocrine insufficiency present Normal or increased if pancreatitis present

Serum canine pancreatic lipase immunoreactivity (cPU)

Normal or increased if pancreatitis present Baseline serum insulin concentration

IDDM: low, normal

NIDDM: low, normal, increased

Insulin resistance induced: low, normal, increased

IDDM, Insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

plication of therapy. Hypoglycemia is most apt to occur as the result of overzealous insulin therapy. The veterinarian must balance the benefits of tight glucose control obtainable with aggressive insulin therapy against the risk of hypoglycemia.

## OVERVIEW OF INSULIN PREPARATIONS

Types of insulin typically used for the home treatment of diabetes in dogs and cats include intermediate-acting insulin (NPH, lente) and long-acting basal insulin (PZI, insulin glargine; (Table 52-2). NPH (Humulin N®, Eli Lilly) is a recombinant human insulin, lente (Vetsulin®, Intervet) is a purified pork-source insulin, and PZI (PZI Vet®, IDEXX) is a beef/pork-source insulin with approximately 90% being beef-source insulin. Insulin glargine (Lantus®, Aventis Pharmaceuticals) is a long-acting insulin analog in which the amino acid sequence has been altered, compared with human



BOX 52-5

Complications of Diabetes Mellitus in Dogs and Cats

#### Common

latrogenic hypoglycemia

Persistent or recurring polyuria, polydipsia, weight loss

Cataracts (dog)

Lens-induced uveitis (dog)

Bacterial infections, especially involving the urinary tract

Chronic pancreatitis

Recurring ketosis, ketoacidosis

Hepatic lipidosis

Peripheral neuropathy (cat)

Systemic hypertension (dog)

#### Uncommon

Peripheral neuropathy (dog)

Diabetic nephropathy

Significant proteinuria

Glomerulosclerosis

Retinopathy

Exocrine pancreatic insufficiency

Gastric paresis

Intestinal hypomotility and diarrhea

Diabetic dermatopathy (i.e., superficial necrolytic dermatitis)

insulin, making glargine more soluble at a slightly acidic pH and less soluble at a physiological pH than human insulin. The solution in the bottle of glargine is acidic, which keeps glargine soluble and suspended in the solution (i.e., the solution is clear, and the bottle does not need to be rolled before the insulin is drawn into the syringe). Because of this dependency on pH, glargine cannot be diluted or mixed with anything that may change the pH of the solution. Glargine forms microprecipitates in the subcutaneous tissue at the site of injection, from which small amounts of insulin glargine are slowly released and absorbed into the circulation. In humans the slow, sustained release of insulin glargine from these microprecipitates results in a relatively constant concentration/time profile over a 24-hour period with no pronounced peak in serum insulin. Insulin glargine is currently recommended as a basal insulin (i.e., sustained long-acting insulin used to inhibit hepatic glucose production) administered once a day at bedtime and used in conjunction with either prandial insulin analogs or oral hypoglycemic drugs in human diabetics.

#### STORAGE AND DILUTION OF INSULIN

Freezing, heating, and shaking the insulin bottle inactivate insulin in the bottle. Although keeping the substance at "room temperature": does not inactivate insulin, I instruct clients to store insulin in the door of the refrigerator to maintain a consistent environment and prolong the life of



Table 52-2

Commonly Used Insulin Preparations for Treating Diabetes in Dogs and Cats

		ADMINISTRATIO	N	TYPICAL DI	JRATION T (hr)	OF	
INSULIN O	ORIGIN	INDICATIONS	ROUTE	FREQUENCY	DOG	CAT	COMMON PROBLEMS
Regular crystalline	Recombinant human	Treat DKA	IV	Continuous infusion	-	-	Rapid decrease in blood glucose concentration
			IM	Hourly initially	4-6	4-6	
			SC	q6-8h <sup>°</sup>	6-8	6-8	May cause hypokalemia
		Treat diabetes at home	SC	q8h	6-8	6-8	<b>7</b> 1
		Treat severe hyperkalemia	SC	Once	_	_	
NPH	Recombinant human	Treat diabetes at home	SC	q12h	8-14	6-12	Short duration of effect in cats
Lente	Pure pork	Treat diabetes at home Good initial insulin for dogs	SC	q12h	8-14	8-14	Short duration of effect in cats
PZI	90% beef 10% pork	Treat diabetes at home Good initial insulin for cats	SC	q12h	_	10-14	Induction of insulin antibodies in dogs
Glargine	Insulin analog	Treat diabetes at home Good initial insulin for cats	SC	q12-24h	10-16	10-16	Duration of effect too long for q12h therapy in some cats

the insulin preparation. Some veterinarians advocate replacing insulin with a new bottle every month to prevent problems caused by loss of activity or sterility. I have not appreciated a clinically significant loss of insulin action with time when insulin preparations, including glargine, are maintained in a constant environment (i.e., refrigerator) and handled appropriately. I do not routinely recommend purchasing a new bottle of insulin every month, especially if the diabetic dog or cat is doing well. However, development of cloudiness or discoloration suggest contamination, change in pH of the solution (glargine), and/or loss of insulin activity. The vial of insulin should be discarded and replaced with a new bottle of insulin. Similarly, loss of insulin activity in the bottle should always be considered whenever clinical signs recur, regardless of the quantity of insulin remaining in the bottle.

Dilution of insulin is a common practice, especially in very small dogs and cats. Although studies evaluating the shelf-life of diluted insulin have not been published, I recommend replacing diluted insulin preparations every 4 to 8 weeks. Even when these guidelines are observed, insufficient amounts of insulin are administered when diluted insulin is used in some dogs and cats, despite appropriate dilution and insulin administration techniques—inadequacies that are corrected when full-strength insulin is used. It is important to remember that insulin glargine is pH dependent and cannot be diluted.

## INITIAL INSULIN RECOMMENDATIONS FOR DIABETIC DOGS

Lente and NPH are the initial insulins of choice for treating diabetes in dogs (see Table 52-2). Recombinant humansource or pork-source insulin should be used to prevent insulin antibodies (see p. 782). My starting dosage for both types of insulin is approximately 0.25 U/kg of body weight. Because the overwhelming majority of diabetic dogs require lente or NPH insulin twice a day, the preference is to start with twice-daily insulin therapy. Establishing control of glycemia is easier and problems with hypoglycemia and the Somogyi response (see p. 780) are less likely when twicedaily insulin therapy is initiated while the insulin dose is low (i.e., at the time insulin treatment is initiated). The initial dosage recommendation (1 U/kg) on the package insert for Vetsulin® is too high. In a recent study by Monroe et al. (2005) evaluating the efficacy of Vetsulin® using the dosage recommendations on the package insert, approximately 40% of the dogs developed clinical signs of hypoglycemia at home and a blood glucose concentration of less than 60 mg/dl was identified in 36% of the dogs during generation of a blood glucose curve in the hospital.

I currently use insulin glargine in poorly controlled diabetic dogs in which NPH and lente insulin are ineffective because of problems with short duration of insulin effect. I rarely use beef/pork-source PZI insulin in dogs because of the potential for development of insulin antibodies directed against the beef insulin in the preparation that may create problems with diabetic control (see p. 782).

#### DIET

Correction of obesity and increasing the fiber content of the diet are the two most beneficial steps that can be taken to improve control of glycemia in diabetic dogs. Obesity causes insulin resistance in dogs and is an important factor accounting for variations in response to insulin therapy in diabetic dogs. Weight loss improves insulin resistance in obese diabetic dogs. Weight loss usually requires a combination of the following: restricting caloric intake, feeding low calorie-dense diets, and increasing caloric expenditure through exercise.

Diets containing increased fiber content are beneficial for treating obesity and improving control of glycemia in diabetics dogs. The ability of the fiber to form a viscous gel appears to be of greatest importance in slowing intestinal glucose absorption. More viscous soluble fibers (e.g., gums, pectin) slow glucose absorption to a greater degree than less viscous insoluble fibers (e.g., cellulose, peanut hulls) and, as such, are believed to be of greater benefit in improving control of glycemia. Most commercial high-fiber diets predominantly contain insoluble fiber, although diets containing mixtures of soluble and insoluble fiber are becoming available. The amount of fiber varies considerably among products, ranging from 3% to 25% of dry matter (normal diets contain less than 2% fiber on a dry matter basis). In general, diets containing 12% or more insoluble fiber or 8% or more of a mixture of soluble and insoluble fiber are most likely to be effective in improving glycemic control in diabetic dogs (Box 52-6).

The dog's susceptibility to the complications of high-fiber diets, its body weight and condition, and the presence of a concurrent disease (e.g., pancreatitis, renal failure) in which diet is an important aspect of therapy ultimately dictate which, if any, fiber diet is fed. Common clinical complications of diets high in insoluble fiber include excessive frequency of defecation, constipation and obstipation, hypoglycemia 1 to 2 weeks after the increase in fiber content of the diet, and refusal to eat the diet. Complications of soluble fiber-containing diets include soft-to-watery stools, excessive flatulence, hypoglycemia 1 to 2 weeks after the increase in fiber content of the diet, and refusal to eat the diet. If firm stools or constipation becomes a problem with diets that are high in insoluble fiber, a mixture of insolubleand soluble-fiber diets can be fed or soluble fiber (e.g., psyllium, canned pumpkin) can be added to the diet to soften the stool. If soft or watery diarrhea or flatulence becomes a problem with soluble fiber-containing diets, an insolublefiber diet can be added and the quantity of the soluble-fiber diet decreased. If palatability is a problem initially, the animal can be gradually switched from its regular diet to a diet containing small amounts of fiber, after which diets containing more fiber are provided. Refusal to consume high-fiber diets months after their initiation is usually a result of boredom with the food. Periodic changes in the types of high-fiber diets and mixtures of diets have been helpful in alleviating this problem. Finally, high-fiber diets should not be fed to thin or emaciated diabetic dogs until control of glycemia is established and a normal body weight attained



## Recommendations for Dietary Treatment of Diabetes Mellitus in Dogs and Cats

Correct obesity and maintain body weight in an acceptable range (see Chapter 54).

Control daily caloric intake.

Increase daily exercise.

Avoid excessive amounts of insulin.

Maintain consistency in the timing and caloric content of the meals.

Feed within the time frame of insulin action.

Feed one half the daily caloric intake at the time of each insulin injection with q12h insulin therapy or at the time of the insulin injection and 8 to 10 hours later with q24h insulin therapy.

Minimize the impact of food on postprandial blood glucose concentrations.

Avoid monosaccharides and disaccharides, propylene glycol, and corn syrup.

Let "nibbler" cats and dogs nibble throughout the day and night; ensure that other pets do not have access to the food. Increase the fiber content of the diet (dogs).

Feed high-protein, low-carbohydrate diets (cats).

### **Veterinary Diets for Diabetic Dogs**

Hill's Prescription Diet w/d
Hill's Prescription Diet r/d (obese diabetic dog)
Purina DCO
Purina OM (obese diabetic dog)
Royal Canin Diabetic HF
Royal Canin Calorie Control CC High Fiber
(obese diabetic dog)
lams Optimum Weight Control

### **Veterinary Diets for Diabetic Cats**

High-protein, low-carbohydrate diets: Purina DM Hill's Prescription Diet MD Royal-Canin Diabetic DS 44

Fiber-containing diets: Hill's Prescription Diet w/d

Hill's Prescription Diet r/d (obese diabetic cat)
Purina OM (obese diabetic cat)
Royal-Canin Calorie Control CC
High Fiber (obese diabetic cat)

using a higher-calorie-dense, lower-fiber diet designed for maintenance.

#### **EXERCISE**

Exercise plays an important role in maintaining glycemic control in the diabetic dog by helping promote weight loss and eliminating the insulin resistance induced by obesity. Exercise also has a glucose-lowering effect by increasing the mobilization of insulin from its injection site, presumably resulting from increased blood and lymph flow, by increasing blood flow (and therefore insulin delivery) to exercising muscles, and by stimulating glucose transporters in muscle cells. The daily routine for diabetic dogs should include exercise, preferably at the same time each day. Strenuous and sporadic exercise can cause severe hypoglycemia and should be avoided. If unavoidable, the insulin dose should be decreased in dogs subjected to sporadic strenuous exercise on those days of anticipated increased exercise. The reduction in insulin dose required to prevent hypoglycemia is variable and determined by trial and error. Reducing the insulin dose by 50% initially is recommended with further adjustments based on the occurrence of symptomatic hypoglycemia and the severity of polyuria and polydipsia that develops during the ensuing 24 to 48 hours. In addition, clients must be aware of the signs of hypoglycemia and have a source of glucose readily available to give their dog should any of these signs develop.

## IDENTIFICATION AND CONTROL OF CONCURRENT PROBLEMS

Concurrent disease and insulin-antagonistic drugs can interfere with tissue responsiveness to insulin, resulting in insulin resistance and poor control of the diabetes. Concurrent disease and insulin-antagonistic drugs typically cause insulin resistance by altering insulin metabolism (prereceptor problem), by decreasing the concentration or binding affinity of insulin receptors on the cell membrane (receptor problem), by interfering with the insulin receptor signaling cascade (postreceptor problem), or by a combination of these. Depending on the etiology, insulin resistance may be mild and easily overcome by increasing the dose of insulin (e.g., obesity); may be severe, causing sustained and marked hyperglycemia regardless of the type and dose of insulin administered (e.g., hyperadrenocorticism); or may fluctuate in severity over time (e.g., chronic pancreatitis; Box 52-7). Some causes of insulin resistance are readily apparent at the time diabetes is diagnosed, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids). Other causes of insulin resistance are not readily apparent and require an extensive diagnostic evaluation to be identified. In general, any concurrent inflammatory, infectious, hormonal, or neoplastic disorder can cause insulin resistance and interfere with the effectiveness of insulin therapy. Identification and treatment of concurrent disease play integral roles in the successful management of the dia-



### Recognized Causes of Insulin Resistance in Diabetic Dogs and Cats

### Disorders Typically Causing Severe Insulin Resistance

Hyperadrenocorticism Acramegaly (cat)

Progesterone excess (diestrus in female dog)

Diabetogenic drugs (most notably glucocorticoids and progestins)

## Disorders Typically Causing Mild or Fluctuating Insulin Resistance

Obesity Infections

Chronic pancreatitis
Chronic inflammation
Disease of the oral cavity

Renal insufficiency Liver insufficiency Cardiac insufficiency Hypothyroidism Hyperthyroidism

Pancreatic exocrine insufficiency

Hyperlipidemia Neoplasia Glucagonoma Pheochromocytom

betic dog. A thorough history, physical examination, and complete diagnostic evaluation are imperative in the newly diagnosed diabetic dog (see the section on diagnosis, p. 769).

## PROTOCOL FOR IDENTIFYING INITIAL INSULIN REQUIREMENTS

Diabetic dogs require several days to equilibrate to changes in insulin dose or preparation. Therefore newly diagnosed diabetic dogs are typically hospitalized for no more than 24 to 48 hours to finish the diagnostic evaluation of the dog and begin insulin therapy. During hospitalization blood glucose concentrations are typically determined at the time insulin is administered and 3, 6, and 9 hours later. The intent is to identify hypoglycemia (i.e., blood glucose less than 80 mg/ dl) in those dogs that are unusually sensitive to the actions of insulin. If hypoglycemia occurs, the insulin dose is decreased before sending the dog home. The insulin dose is not adjusted in those dogs that remain hyperglycemic during the first few days of insulin therapy. The objective during this first visit is not to establish perfect glycemic control before sending the dog home. Rather, the objective is to begin to reverse the metabolic derangements induced by the disease, allow the patient to equilibrate to the insulin and change in diet, teach the client how to administer insulin, and give the client a few days to become accustomed to treating the diabetic dog at home. Adjustments in insulin therapy are made on subsequent evaluations, once the client and pet have become accustomed to the treatment regimen.

Diabetic dogs are typically evaluated once weekly until an effective insulin treatment protocol is identified. Glycemic control is attained when clinical signs of diabetes have resolved; the pet is healthy and interactive in the home; its body weight is stable (unless the dog is undergoing weight loss to correct obesity); the client is satisfied with the prog-

ress of therapy; and, if possible, the blood glucose concentrations range between 100 and 250 mg/dl throughout the day. The client is informed at the time insulin therapy is initiated that it will take approximately 1 month to establish a satisfactory insulin treatment protocol, assuming unidentified insulin-antagonistic disease is not present. The goals of therapy are also explained to the client. During this month changes in insulin dose, type, and frequency of administration are common and should be anticipated by the client. At each evaluation the client's subjective opinion of water intake, urine output, and overall health of the pet is discussed; a complete physical examination is performed; change in body weight noted; and serial blood glucose measurements obtained over an 8- to 12-hour period after insulin administration are assessed. Adjustments in insulin therapy are based on this information, the pet is sent home, and an appointment is scheduled for the next week to reevaluate the response to any change in therapy. If the dog remains poorly controlled, the dose of insulin is gradually increased by 1 to 5 U/injection (depending on the size of the dog) each week until control is attained. This gradual increase in dose helps prevent hypoglycemia and the Somogyi response. Control of glycemia can be established in most dogs using insulin doses in the range of 1.0 U of insulin/kg or less administered twice each day. If the insulin dose exceeds 1.5 U/kg/injection without adequate glycemic control, then further investigations to determine the reason for treatment failure are indicated (see the section on complications of insulin therapy, p. 779). If hypoglycemia is noted either clinically or biochemically at any time, the insulin dosage should be decreased and further adjustments in the insulin dose performed as needed to attain glycemic control.

Many factors affect the dog's glycemic control from day to day, including variations in insulin administration and absorption, dietary indiscretions and caloric intake, amount of exercise, and variables that affect insulin responsiveness (e.g., stress, concurrent inflammation, infection). As a consequence, the insulin dosage required to maintain glycemic control typically changes with time. Initially, a fixed dose of insulin is administered at home and changes are made only after the client consults with the veterinarian. As the insulin dose range required to maintain glycemic control becomes apparent and as confidence is gained in the client's ability to recognize signs of hypoglycemia and hyperglycemia, the client is eventually allowed to make slight adjustments in the insulin dose at home on the basis of clinical observations of the pet's well-being. However, the client is instructed to stay within the agreed-upon insulin dose range. If the insulin dose is at the upper or lower end of the established range and the pet is still symptomatic, the client is instructed to call the veterinarian before making further adjustments in the insulin dose.

## **Techniques for Monitoring Diabetic Control**

The basic objective of insulin therapy is to eliminate the clinical signs of diabetes mellitus while avoiding the common complications associated with the disease (see Box 52-5). Common complications in dogs include blindness caused by cataract formation, weight loss, hypoglycemia, recurring ketosis, and recurrence of polyuria and polydipsia. The devastating chronic complications of human diabetes (e.g., nephropathy, vasculopathy, coronary artery disease) require several decades to develop and are uncommon in diabetic dogs. As such, the need to establish nearly normal blood glucose concentrations is not necessary in diabetic dogs. Generally speaking, most clients are happy and most dogs are healthy and relatively asymptomatic if blood glucose concentrations are kept between 100 and 250 mg/dl.

### HISTORY AND PHYSICAL EXAMINATION

The most important initial parameters for assessing control of glycemia are the client's subjective opinion of severity of clinical signs and overall health of the pet, findings on physical examination, and stability of body weight. If the client is happy with results of treatment, the physical examination is supportive of good glycemic control, and the body weight is stable, the diabetic dog is usually adequately controlled. Measurement of serum fructosamine concentration can add further objective evidence for status of glycemic control (discussed in more detail later). Poor control of glycemia should he suspected and additional diagnostics or a change in insulin therapy considered if the client reports clinical signs suggestive of hyperglycemia or hypoglycemia, the physical examination identifies problems consistent with poor control of glycemia (e.g., thin appearance, poor haircoat), or the dog is losing weight.

## SINGLE BLOOD GLUCOSE DETERMINATION

Measuring a single blood glucose concentration is helpful only if hypoglycemia is identified. Documenting hypoglycemia supports insulin overdosage and the need to decrease the insulin dose, especially if glycemic control is poor (see the discussion of the Somogyi response, p. 780). In contrast, documenting an increased blood glucose concentration does not, by itself, confirm poor control of glycemia. Stress or excitement can cause marked hyperglycemia, which does not reflect the dog's responsiveness to insulin and can lead to the erroneous belief that the diabetic dog is poorly controlled. If a discrepancy exists between the history, physical examination findings, and blood glucose concentration or if the dog is fractious, aggressive, excited, or scared and the blood glucose concentration is known to be unreliable, measurement of serum fructosamine concentration should be done to further evaluate status of glycemic control. In addition, a single blood glucose concentration is not reliable for evaluating the effect of a given insulin type and dose in a poorly controlled diabetic dog (see the section on serial blood glucose curve).

## SERUM FRUCTOSAMINE CONCENTRATION

Fructosamines are glycated proteins that result from an irreversible, nonenzymatic, insulin-independent binding of glucose to serum proteins. The extent of glycosylation of serum proteins is directly related to the blood glucose concentration; the higher the average blood glucose concentration during the preceding 2 to 3 weeks, the higher the serum fructosamine concentration, and vice versa. Serum fructosamine concentration is not affected by acute increases in the blood glucose concentration, as occurs with stress- or excitement-induced hyperglycemia, but can be affected by concurrent hypoalbuminemia (less than 2.5 g/dl), hyperlipidemia (triglycerides greater than 150 mg/dl), or hyperthyroidism (Table 52-3). Serum fructosamine concentrations can be measured during the routine evaluation of glycemic control performed every 3 to 6 months; to clarify the effect of stress or excitement on blood glucose concentrations; to clarify discrepancies between the history, physical examination findings, and serial blood glucose concentrations; and to assess the effectiveness of changes in insulin therapy.

Fructosamine is measured in serum, which should be frozen and shipped on cold packs overnight to the laboratory. Storage of serum at room temperature overnight can decrease serum fructosamine results by 10%. Each laboratory should furnish its own reference range. In our laboratory the normal reference range for serum fructosamine in dogs is 225 to 375 µmol/L; a range determined in healthy dogs with persistently normal blood glucose concentrations. Interpretation of serum fructosamine in a diabetic dog must take into consideration the fact that hyperglycemia is common, even in well-controlled diabetic dogs (see Table 52-3). Most clients are happy with the pet's response to insulin treatment if serum fructosamine concentrations can be kept between 350 and 450 µmol/L. Values greater than 500 µmol/L suggest inadequate control of the diabetic state, and values greater than 600 µmol/L indicate serious lack of glycemic control. Serum fructosamine concentrations in the



**TABLE 52-3** 

Sample Handling, Methodology, and Normal Values for Serum Fructosamine Concentrations Measured in Our Laboratory

	FRUCTOSAMINE
Blood sample	1-2 ml; allow to clot, obtain serum
Sample handling	Freeze until assayed
Methodology	Automated colorimetric assay using nitroblue tetrazolium chloride
Factors affecting results	Hypoalbuminemia (decreased), hyperlipidemia (mild decrease—dogs), azotemia (mild decrease—dogs), hyperthyroidism (decreased—cats), storage at room temperature (decreased)
Normal range	225 to 375 μmol/L (dogs) 190 to 365 μmol/L (cats)
Interpretation in Diabetic Dogs	and Cats
e II	272.402

Excellent control	350-400 μmol/L
Good control	400-450 μmol/L
Fair control	450-500 μmol/L
Poor control	>500 µmol/L
Prolonged hypoglycemia	<300 μmol/L

lower half of the normal reference range (i.e., less than 300 µmol/L) or below the normal reference range should raise concern for significant periods of hypoglycemia in the diabetic dog. Increased serum fructosamine concentrations (i.e., >500 µmol/L) suggest poor control of glycemia and a need for insulin adjustments but do not identify the underlying problem.

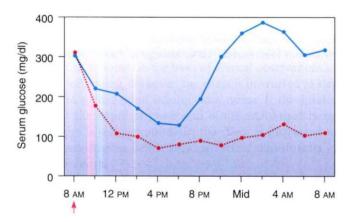
### URINE GLUCOSE MONITORING

Occasional monitoring of urine for glycosuria and ketonuria is helpful in diabetic dogs that have problems with recurring ketosis or hypoglycemia to identify ketonuria or persistent negative glycosuria, respectively. The client is instructed not to adjust daily insulin doses on the basis of morning urine glucose measurements, except to decrease the insulin dose in dogs with recurring hypoglycemia and persistent negative glycosuria. The vast majority of diabetic dogs develop complications because clients were misled by morning urine glucose concentrations. Persistent glycosuria throughout the day and night suggests inadequate control of the diabetic state and the need for a more complete evaluation of diabetic control using other techniques discussed in this section.

### SERIAL BLOOD GLUCOSE CURVES

If an adjustment in insulin therapy is deemed necessary after review of the history, physical examination, changes in body weight, and serum fructosamine concentration, then a serial blood glucose curve should be generated to provide guidance in making the adjustment, unless blood glucose measurements are unreliable because of stress, aggression, or excitement. The serial blood glucose curve provides guidelines for making adjustments in insulin therapy. Evaluation of a serial blood glucose curve is mandatory during the initial regulation of the diabetic dog and is necessary in the dog in which clinical manifestations of hyperglycemia or hypoglycemia have developed. Reliance on history, physical examination, body weight, and serum fructosamine concentration to determine when a blood glucose curve is needed helps reduce the frequency with which blood glucose curves must be performed, thereby minimizing the animal's aversion to these evaluations and improving the chances of obtaining meaningful results when a blood glucose curve is needed.

When a blood glucose curve is being generated, the insulin and feeding schedule used by the client should be maintained, the dog dropped off at the hospital early in the morning, and blood obtained every 1 to 2 hours throughout the day for glucose determination. It is more important to maintain the pet's daily routine than to risk inaccurate blood glucose results caused by inappetence in the hospital or insulin administration at an unusual time (Fig. 52-2). If there are concerns regarding the client's technique for administering insulin, the client can administer insulin (using his or her own insulin and syringe) in the hospital after the initial blood glucose is obtained or can demonstrate his or her technique using sterile saline after arriving to pick up the pet at the end of the day. The veterinarian or a veterinary technician should closely evaluate the entire insulin administration procedure. By measuring blood glucose concentration every 1 to 2 hours throughout the day, the clinician will be able to determine if the insulin is effective and identify the glucose nadir, time of peak insulin effect, duration of insulin effect, and severity of fluctuation in blood glucose concentrations in that particular dog. Determining the glucose nadir and the time of the glucose nadir in relation to the time of insulin administration is critical for assessing the duration of insulin effect. If the glucose nadir has not been identified by the time of the next insulin injection, the glucose curve should be continued, the scheduled insulin injection aborted, and the dog fed its evening meal (see the discussion of the prolonged duration of insulin effect, p. 781). Obtaining only 1 or 2 blood glucose concentrations has not been reliable for evaluating the effect of a given insulin dose (Fig. 52-3). Persistent poor control of the dia-



Mean blood glucose concentrations in eight diabetic dogs after the administration of NPH insulin (1) and the feeding of equal-sized meals at 8 AM and 6 PM (blue line) or feeding them nothing (red line) during the 24 hours of blood sampling.

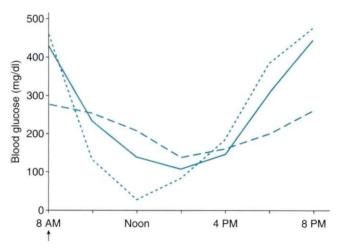


FIG 52-3

Blood glucose concentration curve in a Dachshund receiving 0.8 U of recombinant human lente insulin per kilogram of body weight twice a day (solid line), a Miniature Poodle receiving 0.6 U of recombinant human lente insulin per kilogram of body weight twice a day (dashed line), and a Terrier-mix receiving 1.1 U of recombinant human lente insulin per kilogram of body weight twice a day (dotted line). Insulin and food was given to each dog at 8 AM. Interpretation of the blood glucose curves suggest short duration of insulin effect in the Dachshund, insulin underdosing in the Miniature Poodle, and the Somogyi response in the Terrier-mix. The blood glucose concentrations were similar in all dogs at 2 PM and 4 PM; the glucose results at these times do not establish the diagnosis in any of the dogs.

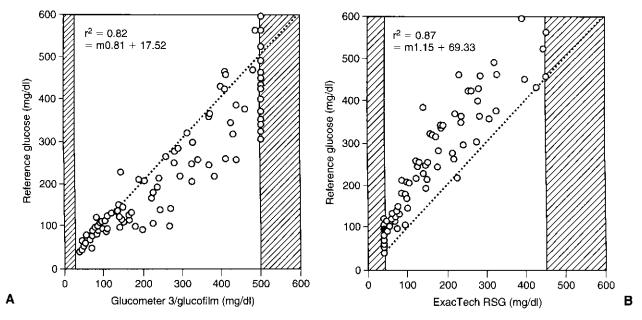
betic state often stems from misinterpretation of the effects of insulin that is based on assessment of only 1 or 2 blood glucose concentrations.

Blood glucose concentrations are typically determined by a point-of-care glucose analyzer or hand-held portable blood glucose monitoring device. Commercially available portable blood glucose-monitoring devices provide blood glucose concentrations that are reasonably close to those obtained with reference methods, although results often overestimate or underestimate actual glucose values. Blood glucose values determined by most portable blood glucose monitoring devices are typically lower than actual glucose values determined by reference methods (Fig. 52-4). This may result in an incorrect diagnosis of hypoglycemia or the misperception that glycemic control is better than it actually is. Failure to consider this error could result in insulin underdosage and the potential for persistence of clinical signs despite apparently acceptable blood glucose results. One exception is the AlphaTRAK® by Abbott Laboratories. Accuracy of this portable glucometer is very good, but glucose values may be higher or lower than glucose values measured by benchtop methodologies on the same blood sample, forcing the veterinarian to accept the blood glucose concentration at face

Insulin therapy is adjusted according to interpretation of a single serial blood glucose curve, and the impact of the change is initially assessed by client perceptions of clinical response and change in serum fructosamine concentration. If problems persist, the blood glucose curve can be repeated. If possible, performing blood glucose curves on multiple, consecutive days should be avoided because it promotes stress-induced hyperglycemia. Information gained from a prior serial blood glucose curve should never be assumed to be reproducible on subsequent curves. Lack of consistency in the results of serial blood glucose curves is a source of frustration for many veterinarians. This lack of consistency is a direct reflection of all the variables that affect the blood glucose concentration in diabetics. Daily self-monitoring of blood glucose concentrations and adjustments in insulin dose are used in human diabetics to minimize the effect of these variables on control of glycemia. A similar approach for diabetic dogs and cats will undoubtedly become more common in the future, as home glucose monitoring techniques are refined. For now, initial assessment of control of glycemia is based on the client's perception of the diabetic pet's health combined with periodic examinations by the veterinarian. Serial blood glucose measurements are indicated if poor control of glycemia is suspected. The goal of serial blood glucose measurements is to obtain a glimpse of the actions of insulin in that diabetic animal and identify a possible reason that the diabetic dog is poorly controlled.

## Protocol for Generating the Serial Blood Glucose Curve at Home

Hyperglycemia induced by stress, aggression, or excitement is the single biggest problem affecting accuracy of the serial blood glucose curve, especially in cats (Fig. 52-5). The biggest



#### FIG 52-4

Scatter plots of blood glucose concentrations obtained with two portable blood-glucose meters versus concentrations obtained using a reference method. Data represent 110 blood samples from 34 dogs. Shaded areas represent concentrations greater than or less than the concentrations that can be detected by each meter. The dashed line represents the theoretical line of equality. Note that one glucose meter tends to read higher (A) and one glucose meter tends to read lower (B) than the reference concentration. (From Cohn LA et al: Assessment of five portable blood glucose meters, a point-of-care analyzer, and color test strips for measuring blood glucose concentration in dogs, J Am Vet Med Assoc 216:198, 2000.)

factors inducing stress-induced hyperglycemia are hospitalization and multiple venipunctures. An alternative to hospital-generated blood glucose curves is to have the client generate the blood glucose curve at home using the ear or lip prick technique and a portable home glucose-monitoring device that allows the client to touch the drop of blood on the ear or lip with the end of the glucose test strip. This technique is usually reserved for diabetic dogs in which the reliability of blood glucose results generated in the veterinary hospital is questionable. The reader is referred to p. 792 for more information on monitoring blood glucose concentrations at home.

#### Interpreting the Serial Blood Glucose Curve

An overview of interpreting results of a serial blood glucose curve is provided in Fig. 52-6. The *ideal* goal is to maintain the blood glucose concentration between 100 mg/dl and 250 mg/dl throughout the day and night, although many diabetic dogs do well despite blood glucose concentrations consistently in the high 100's to low 300's. Typically, the highest blood glucose concentrations occur at the time of each insulin injection, but this does not always occur. If the blood glucose nadir is greater than 150 mg/dl, the insulin dose may need to be increased, and if the nadir is less than 80 mg/dl, the insulin dose should be decreased.

Duration of insulin effect can be assessed if the glucose nadir is greater than 80 mg/dl and there has not been a rapid decrease in the blood glucose concentration after insulin administration. Assessment of duration of insulin effect may not be valid when the blood glucose decreases to less than 80 mg/dl or decreases rapidly because of the potential induction of the Somogyi response, which can falsely decrease the apparent duration of insulin effect (see p. 780). A rough approximation of the duration of effect of insulin can be gained by examining the time of the glucose nadir. For most well-controlled diabetic dogs, the initial blood glucose concentration near the time of insulin administration is less than 300 mg/dl and the glucose nadir occurs 8 to 10 hours after injection of insulin. An initial blood glucose concentration greater than 300 mg/dl, combined with a glucose nadir occurring less than 8 hours after insulin administration and subsequent blood glucose concentrations exceeding 250 mg/ dl, is supportive of short duration of insulin effect (see p. 781). A glucose nadir occurring 12 hours or longer after insulin administration is supportive of prolonged duration of insulin effect (see p. 781). Dogs may develop hypoglycemia or the Somogyi response if the duration of insulin effect is greater than 14 hours and the insulin is being administered twice a day (Fig. 52-7).

## Role of Serum Fructosamine in Aggressive, Excitable, or Stressed Dogs

Blood glucose curves are unreliable in aggressive, excitable, or stressed dogs because of problems related to stress-induced

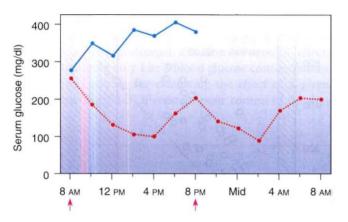


FIG 52-5

Blood glucose concentration curves in a fractious Terriermix. The same dose of NPH insulin was given for each curve. One glucose curve (blue line) was obtained with the dog in an agitated state requiring physical restraint each time a blood specimen was obtained; blood for the other glucose curve (red line) was obtained through a jugular catheter with minimal-to-no restraint and the dog in a quiet state. 1, Insulin administration and food.

hyperglycemia. In these dogs the clinician must make an educated guess as to where the problem lies (e.g., wrong type of insulin, low dose), make an adjustment in therapy, and rely on changes in serum fructosamine to assess the benefit of the change in treatment. The reader is referred to p. 792 for more information on the use of serum fructosamine in diabetic pets with stress-induced hyperglycemia.

#### **INSULIN THERAPY DURING SURGERY**

Generally, surgery should be delayed in diabetic dogs until the animal's clinical condition is stable and the diabetic state is controlled with insulin. The exception are those situations in which surgery is required to eliminate insulin resistance (e.g., ovariohysterectomy in a diestrus bitch) or to save the animal's life. The surgery itself does not pose a greater risk in a stable diabetic animal than in a nondiabetic animal. The concern is the interplay between insulin therapy and the lack of food intake during the perioperative period. The stress of anesthesia and surgery also causes the release of diabetogenic hormones, which promote ketogenesis. Insulin must be administered during the perioperative period to prevent

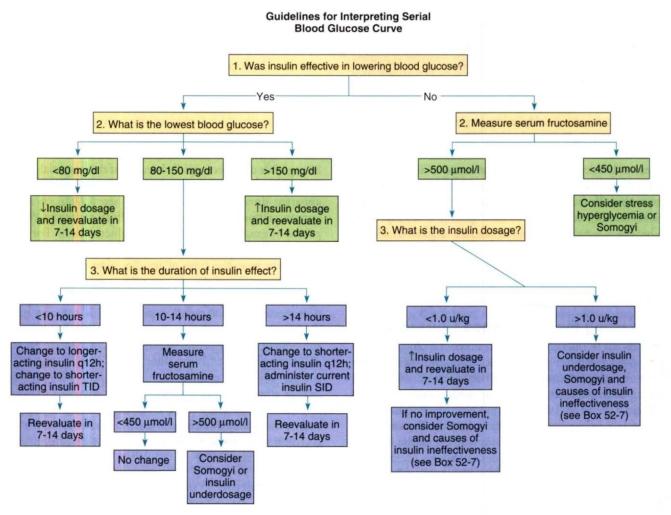
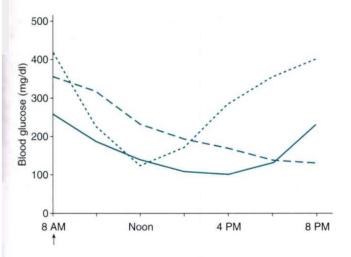


FIG 52-6
Algorithm for interpreting results of a blood glucose concentration curve.



#### FIG 52-7

Blood glucose concentration curves obtained from three diabetic dogs treated with recombinant human lente insulin twice a day, illustrating a difference between dogs in the duration of insulin effect. The insulin is effective in lowering the blood glucose concentration in all dogs, and the blood glucose nadir is between 100 and 175 mg/dl for the dogs. However, the duration of insulin effect is approximately 12 hours (solid line) in one dog with good control of glycemia (ideal duration of effect), approximately 8 hours (dotted line) in one dog with persistently poor control of glycemia (short duration of effect), and greater than 12 hours (dashed line) in one dog with a history of good days and bad days of glycemic control (prolonged duration of effect)—a history suggestive of the Somogyi response (see Fig. 52-8).

severe hyperglycemia and minimize ketone formation. To compensate for the lack of food intake and prevent hypoglycemia, the amount of insulin administered during the perioperative period is decreased and IV dextrose is administered when needed.

The following protocol is used during the perioperative period in dogs and cats undergoing surgery. The day before surgery the dog or cat is given its normal dose of insulin and fed as usual. Food is withheld after 10 PM. On the morning of the procedure the blood glucose concentration is measured before the dog or cat is given insulin. If the blood glucose concentration is less than 100 mg/dl, insulin is not given and an IV infusion of 2.5% to 5% dextrose is initiated. If the blood glucose concentration is between 100 and 200 mg/dl, one quarter of the animal's usual morning dose of insulin is given and an IV infusion of dextrose is initiated. If the blood glucose concentration is more than 200 mg/dl, one half of the usual morning dose of insulin is given but the IV dextrose infusion is withheld until the blood glucose concentration is less than 150 mg/dl. In all three situations the blood glucose concentration is measured every 30 to 60 minutes during the surgical procedure. The goal is to maintain the blood glucose concentration between 150 and 250 mg/dl during the perioperative period. A 2.5% to 5% dextrose infusion is administered intravenously as needed to correct or prevent hypoglycemia.

When the blood glucose concentration exceeds 300 mg/dl, the dextrose infusion should be discontinued and the blood glucose concentration evaluated 30 and 60 minutes later. If the blood glucose concentration remains greater than 300 mg/dl, regular crystalline insulin is administered intramuscularly at approximately 20% of the dose of long-acting insulin being used at home. Subsequent doses of regular crystalline insulin should be given no more frequently than every 4 hours, and the dose should be adjusted on the basis of the effect of the first insulin injection on the blood glucose concentration.

On the day after surgery the diabetic dog or cat can usually be returned to the routine schedule of insulin administration and feeding. An animal that is not eating can be maintained with IV dextrose infusions and regular crystalline insulin injections given subcutaneously every 6 to 8 hours. Once the animal is eating regularly, it can be returned to its normal insulin and feeding schedule.

# **COMPLICATIONS OF INSULIN THERAPY** Hypoglycemia

Hypoglycemia is a common complication of insulin therapy. Signs of hypoglycemia are most apt to occur after sudden large increases in the insulin dose, with excessive overlap of insulin action in dogs receiving insulin twice a day, after prolonged inappetence, during unusually strenuous exercise, following sudden improvement in concurrent insulin resistance, and in insulin-treated cats that have reverted to a non-insulin-dependent state (see p. 785). In these situations severe hypoglycemia may occur before glucose counterregulation (i.e., secretion of glucagon, epinephrine, cortisol, and growth hormone) is able to compensate for and reverse hypoglycemia. The occurrence and severity of clinical signs is dependent on the rate of blood glucose decline and the severity of hypoglycemia. In many diabetic dogs signs of hypoglycemia are not apparent to clients, and hypoglycemia is identified during evaluation of a serial blood glucose curve or suspected when a low serum fructosamine concentration is identified. Clinical signs and treatment of hypoglycemia are discussed on p. 765. If clinical signs of hypoglycemia have occurred, insulin therapy should be stopped until hyperglycemia and glycosuria recur. The adjustment in the insulin dose is somewhat arbitrary; as a general rule of thumb, the insulin dose initially should be decreased 25% to 50% and subsequent adjustments in the dose based on clinical response and results of blood glucose measurements. Failure of glycosuria to recur after a hypoglycemic episode suggests reversion to a non-insulin-dependent diabetic state or impaired glucose counterregulation.

### **Recurrence of Clinical Signs**

Recurrence or persistence of clinical signs is perhaps the most common complication of insulin therapy in diabetic dogs. This is usually caused by problems with client technique in administering insulin; problems with insulin therapy relating to the insulin type, dose, species, or frequency of administration; or problems with responsiveness

to insulin caused by concurrent inflammatory, infectious, neoplastic, or hormonal disorders (i.e., insulin resistance).

**Problems with client administration and insulin activity.** Failure to administer an appropriate dose of biologically active insulin will result in recurrence or persistence of clinical signs. Common reasons include administration of biologically inactive insulin (e.g., outdated, overheated, previously frozen, destroyed by shaking the bottle), administration of diluted insulin, use of inappropriate insulin syringes for the concentration of insulin (e.g., U100 syringe with U40 insulin), or problems with insulin administration technique (e.g., failure to correctly read the insulin syringe, inappropriate injection technique). These problems are identified by evaluating the client's insulin administration technique and by administering new, undiluted insulin and measuring several blood glucose concentrations throughout the day.

**Problems with the insulin treatment regimen.** The most common problems with the insulin treatment regimen in the dog include insulin underdosage, insulin overdosage causing the Somogyi response, short duration of effect of lente or NPH insulin, and once-daily insulin administration. The insulin treatment regimen should be critically evaluated for possible problems in these areas and appropriate changes made in an attempt to improve insulin effectiveness, especially if the history and physical examination do not suggest a concurrent disorder causing insulin resistance.

**Diluted insulin.** Diluted insulin should be replaced with full-strength insulin. In some dogs insufficient amounts of insulin are administered when diluted insulin is used, despite appropriate dilution and insulin administration techniques. These inadequacies are corrected when full-strength insulin is used.

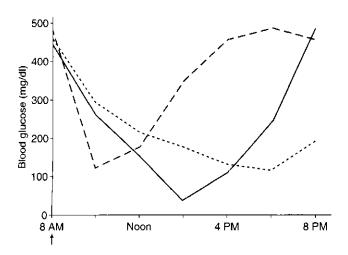
**Insulin underdosing.** Control of glycemia can be established in most dogs using less than 1.0 U of insulin/kg of body weight administered twice daily. An inadequate dose of insulin in conjunction with once-daily insulin therapy is a common cause for persistence of clinical signs. In general, insulin underdosing should be considered if the insulin dose is less than 1.0 U/kg and the animal is receiving insulin twice a day. If insulin underdosing is suspected, the dose of insulin should be gradually increased by 1 to 5 U/ injection (depending on the size of the dog) per week. The effectiveness of the change in therapy should be evaluated by client perception of clinical response and measurement of serum fructosamine or serial blood glucose concentrations. Other causes for insulin ineffectiveness, most notably the Somogyi response, should be considered once the insulin dose exceeds 1.0 to 1.5 U/kg/injection, the insulin is being administered every 12 hours, and control of glycemia remains poor.

Insulin overdosing and the Somogyi response. The Somogyi response results from a normal physiologic response to impending hypoglycemia induced by excessive insulin. When the blood glucose concentration declines to less than 65 mg/dl or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct

hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones, most notably epinephrine and glucagon, increase the blood glucose concentration, minimize signs of hypoglycemia, and cause marked hyperglycemia within 12 hours of glucose counterregulation. The marked hyperglycemia that occurs after hypoglycemia is due, in part, to an inability of the diabetic dog to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration. By the next morning the blood glucose concentration can be extremely elevated (greater than 400 mg/dl), and the morning urine glucose concentration is consistently 1 to 2 gm/dl as measured with urine glucose test strips. Unrecognized short duration of insulin effect, combined with insulin dose adjustments based on morning urine glucose concentrations, is historically the most common cause for the Somogyi response in dogs.

Clinical signs of hypoglycemia are typically mild or not recognized by the client; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces the Somogyi response is variable and unpredictable. The Somogyi response is often suspected in poorly controlled diabetic dogs in which insulin dosage is approaching 2.2 U/kg body weight/injection but can also occur at insulin dosages less than 0.5 U/kg/injection. Toy and miniature breeds of dogs are especially susceptible to development of the Somogyi response with lower-than-expected doses of insulin.

The diagnosis of the Somogyi response requires demonstration of hypoglycemia (less than 80 mg/dl) followed by hyperglycemia (greater than 300 mg/dl) after insulin administration (Fig. 52-8). The Somogyi response should also be suspected when the blood glucose concentration decreases rapidly regardless of the glucose nadir (e.g., a drop from 400 to 100 mg/dl in 2 to 3 hours). If the duration of insulin effect is greater than 12 hours, hypoglycemia often occurs at night after the evening dose of insulin and the serum glucose concentration is typically greater than 300 mg/dl the next morning. Unfortunately, the diagnosis of the Somogyi response can be elusive, in part because of the effects of the diabetogenic hormones on blood glucose concentrations after an episode of glucose counterregulation. Secretion of diabetogenic hormones during the Somogyi response may induce insulin resistance, which can last 24 to 72 hours after the hypoglycemic episode (Fig. 52-9). If a serial blood glucose curve is obtained on the day glucose counterregulation occurs, hypoglycemia will be identified and the diagnosis established. However, if the serial blood glucose curve is obtained on a day when insulin resistance predominates, hypoglycemia will not be identified and the insulin dose may be incorrectly increased in response to the high blood glucose values. A cyclic history of one or two days of good glycemic control followed by several days of poor control should raise suspicion for insulin resistance caused by glucose counterregulation. Serum fructosamine concentrations are unpredictable but are usually increased (>500 µmol/L)-results that confirm poor glycemic control but do not identify the underlying cause.



#### FIG 52-8

Blood glucose concentration curves obtained from three poorly controlled diabetic dogs treated with recombinant human lente insulin twice a day, illustrating the typical blood glucose curves suggestive of the Somogyi response. In one dog (solid line) the glucose nadir is less than 80 mg/ dl and is followed by a rapid increase in the blood glucose concentration. In one dog (dashed line) a rapid decrease in the blood glucose concentration occurs within 2 hours of insulin administration and is followed by a rapid increase in the blood glucose concentration; the rapid decrease in blood glucose stimulates glucose counterregulation, despite maintaining the blood glucose nadir above 80 mg/dl. In one dog (dotted line) the blood glucose curve is not suggestive of the Somogyi response, per se. However, the insulin injection causes the blood glucose to decrease by approximately 300 mg/dl during the day, and the blood glucose concentration at the time of the evening insulin injection is considerably lower than the 8 AM blood glucose concentration. If a similar decrease in the blood glucose occurs with the evening insulin injection, hypoglycemia and the Somogyi response would occur at night and would explain the high blood glucose concentration in the morning and the poor control of the diabetic state.

Establishing the diagnosis may require several days of hospitalization and serial blood glucose curves, an approach that eventually leads to problems with stress-induced hyperglycemia. An alternative, preferable approach is to arbitrarily reduce the insulin dose 1 to 5 units and have the client evaluate the dog's clinical response over the ensuing 2 to 5 days. If clinical signs of diabetes worsen after a reduction in the insulin dose, another cause for the insulin ineffectiveness should be pursued. However, if the client reports no change or improvement in clinical signs, continued gradual reduction of the insulin dose should be pursued. Alternatively, glycemic regulation of the diabetic dog could be started over using an insulin dose of 0.25 U/kg given twice daily.

**Short duration of insulin effect.** For most dogs, the duration of effect of lente and NPH insulin is 10 to 14 hours and twice-daily insulin administration is effective in controlling blood glucose concentrations. However, in some diabetic dogs the duration of effect of lente and NPH insulin is less than 10 hours, a duration that is too short to prevent

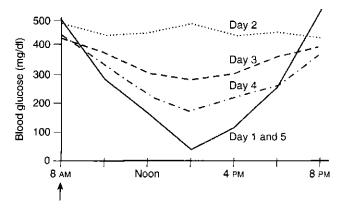


FIG 52-9

Schematic of the change in the results of blood glucose curves obtained an sequential days after induction of the Somogyi response to hypoglycemia induced by an overdose of insulin. Hypoglycemia and the Somogyi response occur on day 1. The secretion of diabetogenic hormones in response to the hypoglycemia causes insulin resistance and increased blood glucose concentrations on day 2. Insulin resistance gradually wanes over the ensuing couple of days (days 3 and 4), eventually resulting in hypoglycemia and the Somogyi response (day 5) as sensitivity to insulin returns to normal. The same dose of insulin is administered each day (arrow).

periods of hyperglycemia and persistence of clinical signs (Fig. 52-10). A diagnosis of short duration of insulin effect is made by demonstrating an initial blood glucose concentration greater than 300 mg/dl combined with a glucose nadir above 80 mg/dl that occurs less than 8 hours after insulin administration and recurrence of hyperglycemia (greater than 250 mg/dl) within 10 hours of the insulin injection (see Fig. 52-7). Treatment involves changing to a longer-acting insulin (e.g., switching to insulin glargine; Fig. 52-11) or increasing the frequency of insulin administration (e.g., initiating therapy q8h). PZI insulin of beef/pork source should not be used in dogs because of potential problems with insulin antibodies (discussed later).

Prolonged duration of insulin effect. In some diabetic dogs the duration of effect of lente or NPH insulin is greater than 12 hours, and twice-daily insulin administration creates problems with hypoglycemia and the Somogyi response. In these dogs the glucose nadir after the morning administration of insulin typically occurs near or after the time of the evening insulin administration, and the morning blood glucose concentration is usually greater than 300 mg/ dl (see Fig. 52-7). The effectiveness of insulin in lowering the blood glucose concentration is variable from day to day, presumably because of varying concentrations of diabetogenic hormones, the secretion of which was induced by prior hypoglycemia. Serum fructosamine concentrations are variable but usually greater than 500 µmol/L. An effective treatment depends, in part, on the duration of effect of the insulin. A 24-hour blood glucose curve should be generated after administration of insulin once in the morning and feeding the dog at the normal times of the day. This will

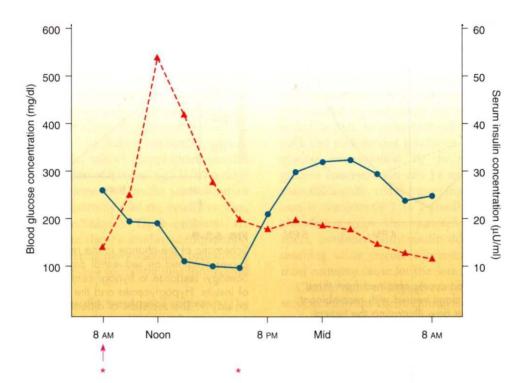


FIG 52-10

Mean blood glucose (blue line) and serum insulin (red line) concentrations in eight dogs with diabetes mellitus treated with a beef-pork source NPH insulin subcutaneously once daily. The duration of NPH effect is too short, resulting in prolonged periods of hyperglycemia beginning shortly after the evening meal. 1, Insulin injection; \*, equal-sized meals consumed.

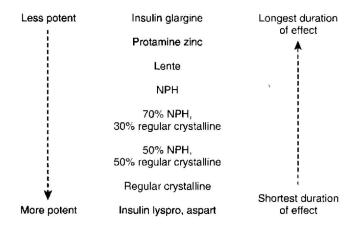


FIG 52-11
Categorization of types of commercial insulin based on the potency and duration of effect. An inverse relationship exists between the potency and duration of effect.

allow the clinician to estimate the duration of effect of the insulin. If the duration of effect is less than 16 hours, a shorter-acting insulin given twice a day or a lower dose of the same insulin given in the evening, compared with the morning insulin dose, can be tried (see Fig. 52-11). If the duration of effect is 16 hours or longer, switching to a longer-acting insulin administered once a day or administering NPH or lente insulin in the morning and regular crystalline

insulin at bedtime (i.e., 16 to 18 hours after the morning insulin injection) can be tried. When different types of insulin are used in the same 24-hour period, the goal is to have the combined duration of effect of the insulins equal 24 hours. Differences in potency of intermediate- and long-acting insulins versus regular crystalline insulin often necessitate use of different dosages for the morning and evening insulin injection; because regular crystalline insulin is more potent, less of it is required to get the same glycemic effect, compared with lente, NPH, PZI, and glargine insulin.

**Inadequate insulin absorption.** Slow or inadequate absorption of ultralente insulin was a problem in dogs and cats, but ultralente insulin is no longer commercially available. A similar problem is uncommon in diabetic dogs treated with NPH or lente insulin. Impaired absorption of insulin may also occur as a result of thickening of the skin and inflammation of the subcutaneous tissues caused by chronic injection of insulin in the same area of the body. Rotation of the injection site will help prevent this problem.

**Circulating insulin-binding antibodies.** Insulin antibodies result from repeated injections of a foreign protein (i.e., insulin). The structure and amino acid sequence of the injected insulin relative to the native endogenous insulin influence the development of insulin antibodies. Conformational insulin epitopes are believed to be more important in the development of insulin antibodies than differences in the

linear subunits of the insulin molecule, per se. The more divergent the insulin molecule being administered from the species being treated, the greater the likelihood that significant amounts of insulin antibodies will be formed. Canine, porcine, and recombinant human insulin are similar, and development of insulin antibodies is uncommon in dogs treated with porcine or recombinant human insulin. In contrast, canine and beef insulin differ and serum insulin antibodies have been identified in 40% to 65% of dogs treated with beef/pork or beef insulin. The presence of serum insulin antibodies is often associated with erratic and poor diabetic control, frequent adjustments in the insulin dose to improve control, and occasional development of severe insulin resistance. Dogs treated with porcine or recombinant human insulin have more stable control of glycemia for extended periods of time compared with dogs treated with beef insulin. Although uncommon, insulin antibodies can develop in dogs treated with recombinant human insulin and should be suspected as the cause of poor glycemic control when another cause cannot be identified. Documentation of serum insulin antibodies should make use of assays that have been validated in diabetic dogs. A switch to porcine-source insulin, a switch to a purer form of insulin (i.e., regular crystalline insulin), or both should be considered if insulin antibodies are identified in a poorly controlled diabetic dog.

Allergic reactions to insulin. Significant reactions to insulin occur in as many as 5% of human diabetics treated with insulin and include erythema, pruritus, induration, and lipoatrophy at the injection site. Allergic reactions to insulin have been poorly documented in diabetic dogs and cats. Pain on injection of insulin is usually caused by inappropriate injection technique, inappropriate site of injection, a reaction to the cold temperature of insulin stored in the refrigerator, or issues with behavior and not an adverse reaction to insulin, per se. Rarely, diabetic dogs and cats will develop focal subcutaneous edema and swelling at the site of insulin injection. Insulin allergy is suspected in these animals. Treatment includes switching to a less antigenic insulin and to a more purified insulin preparation (e.g., regular crystalline insulin). Systemic allergic reactions to insulin in dogs or cats have vet to be identified.

Concurrent disorders causing insulin resistance. Insulin resistance is a condition in which a normal amount of insulin produces a subnormal biologic response. Insulin resistance may result from problems occurring before the interaction of insulin with its receptor, at the receptor, or at steps distal to the interaction of insulin and its receptor. No insulin dose clearly defines insulin resistance. For most diabetic dogs control of glycemia can usually be attained using 1.0 U or less of NPH or lente insulin per kilogram of body weight given twice daily. Insulin resistance should be suspected if control of glycemia is poor despite an insulin dosage in excess of 1.5 U/kg, when excessive amounts of insulin (i.e., insulin dosage >1.5 U/kg) are necessary to maintain the blood glucose concentration below 300 mg/dl, and when control of glycemia is erratic and insulin requirements are constantly changing in an attempt to maintain control of glycemia. Failure of the blood glucose concentration to decrease below 300 mg/dl during a serial blood glucose curve is suggestive of, but not definitive for, the presence of insulin resistance. An insulin resistance–type blood glucose curve can also result from stress-induced hyperglycemia, the Somogyi response, and other problems with insulin therapy, and a decrease in the blood glucose concentration below 300 mg/dl can occur with disorders causing relatively mild insulin resistance. Serum fructosamine concentrations are typically greater than 500  $\mu$ mol/L in dogs with insulin resistance and can exceed 700  $\mu$ mol/L if resistance is severe.

Many disorders can interfere with insulin action (see Box 52-7). The most common in diabetic dogs include diabetogenic drugs (i.e., glucocorticoids), severe obesity, hyperadrenocorticism, diestrus, chronic pancreatitis, renal insufficiency, oral and urinary tract infections, hyperlipidemia, and insulin antibodies in dogs treated with beef insulin. Obtaining a complete history and performing a thorough physical examination is the most important step in identifying these concurrent disorders. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum pancreatic lipase immunoreactivity, serum progesterone concentration (intact female dog), abdominal ultrasound, and urinalysis with bacterial culture should be obtained to further screen for concurrent illness. Additional tests will be dependent on results of the initial screening tests (Box 52-8).

## CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Complications resulting from diabetes or its treatment are common in diabetic dogs and include blindness and anterior uveitis resulting from cataract formation, hypoglycemia, chronic pancreatitis, recurring infections, poor glycemic control, and ketoacidosis (see Box 52-5). Many clients are hesitant to treat their newly diagnosed diabetic dog because of knowledge regarding chronic complications experienced in human diabetics and concern that a similar fate awaits their pet. However, clients should be assured that the devastating effects of human diabetes (e.g., nephropathy, vasculopathy, coronary artery disease) require 10 to 20 years or longer to develop and therefore are uncommon in diabetic dogs.

### **Cataracts**

Cataract formation is the most common and one of the most important long-term complications of diabetes mellitus in the dog. A retrospective-cohort study on the development of cataracts in 132 diabetic dogs referred to a university referral hospital found cataract formation in 14% of dogs at the time diabetes was diagnosed and a time interval for 25%, 50%, 75%, and 80% of the study population to develop cataracts at 60, 170, 370, and 470 days, respectively (Beam et al., 1999). The pathogenesis of diabetic cataract formation is thought to be related to altered osmotic relationships in the lens induced by the accumulation of sorbitol and fructose, sugars that are potent hydrophilic agents and cause an influx of



BOX 52-8

Diagnostic Tests to Consider for the Evaluation of Insulin Resistance in Diabetic Dogs and Cats

Complete blood count, serum biochemistry panel, urinalysis Bacterial culture of the urine

Plasma lipase immunoreactivity (PLI) (pancreatitis)

Serum trypsin-like immunoreactivity (TLI) (exocrine pancreatic insufficiency)

Adrenocortical function tests

Urine cortisol:creatinine ratio (spontaneous hyperadrenocorticism)

Low-dose dexamethasone suppression test (spontaneous hyperadrenocorticism)

ACTH-stimulation test (iatrogenic hyperadrenocorticism) Thyroid function tests

Baseline serum total and free thyroxine (hypothyroidism and hyperthyroidism)

Endogenous thyroid-stimulating hormone (hypothyroidism)

Serum progesterone concentration (diestrus in intact female dog)

Fasting serum triglyceride concentration (hyperlipidemia)
Plasma growth hormone or serum insulin-like growth factor
I concentration (acromegaly)

Serum insulin concentration 24 hours after discontinuation of insulin therapy (insulin antibodies)

Abdominal ultrasonography (adrenomegaly, adrenal mass, pancreatitis, pancreatic mass)

Thoracic radiography (cardiomegaly, neoplasia)

Computed tomography or magnetic resonance imaging (pituitary mass)

water into the lens, leading to swelling and rupture of the lens fibers and the development of cataracts. Cataract formation is an irreversible process once it begins, and it can occur quite rapidly. Diabetic dogs that are poorly controlled and have problems with wide fluctuations in the blood glucose concentration seem especially at risk for rapid development of cataracts. Blindness may be eliminated by removing the abnormal lens. Vision is restored in approximately 75% to 80% of diabetic dogs that undergo cataract removal. Factors that affect the success of surgery include the degree of glycemic control preceding surgery, presence of retinal disease, and presence of lens-induced uveitis. Acquired retinal degeneration affecting vision is more of a concern in older diabetic dogs than is diabetic retinopathy. Fortunately, acquired retinal degeneration is unlikely in an older diabetic dog with vision immediately before cataract formation. If available, electroretinography should be performed before surgery to evaluate retinal function.

### **Lens-Induced Uveitis**

During embryogenesis the lens is formed within its own capsule, and its structural proteins are not exposed to the immune system. Therefore immune tolerance to the crystalline proteins does not develop. During cataract formation and reabsorption lens proteins are exposed to the local immune system, resulting in inflammation and uveitis. Uveitis that occurs in association with a reabsorbing, hypermature cataract may decrease the success of cataract surgery and must be controlled before surgery. The treatment of lens-induced uveitis focuses on decreasing the inflammation and preventing further intraocular damage. Topical ophthalmic corticosteroids are the most commonly used drug for the control of ocular inflammation. However, systemic absorption of topically applied corticosteroids may cause insulin resistance and interfere with glycemic control of the diabetic state, especially in toy and miniature breeds. An alternative is the topical administration of nonsteroidal antiinflammatory agents (e.g., 0.03% flurbiprofen) or cyclosporine.

## **Diabetic Neuropathy**

Although a common complication in the diabetic cat (see p. 795), diabetic neuropathy is infrequently recognized in the diabetic dog. Subclinical neuropathy is probably more common than is severe neuropathy resulting in clinical signs. Clinical signs consistent with diabetic neuropathy are most commonly recognized in dogs that have been diabetic for a long time (i.e., 5 years or longer). Clinical signs and physical examination findings include weakness, knuckling, abnormal gait, muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. Diabetic neuropathy in the dog is primarily a distal polyneuropathy, characterized by segmental demyelination and remyelination and axonal degeneration and regeneration. There is no specific treatment for diabetic neuropathy besides meticulous metabolic control of the diabetic state.

### **Diabetic Nephropathy**

Although diabetic nephropathy has occasionally been reported in the dog, its clinical recognition appears to be low. Histopathologic findings include membranous glomerulonephropathy, glomerular and tubular basement membrane thickening, an increase in the mesangial matrix material, the presence of subendothelial deposits, glomerular fibrosis, and glomerulosclerosis. The pathogenic mechanism of diabetic nephropathy is unknown. Clinical signs depend on the severity of glomerulosclerosis and the functional ability of the kidney to excrete metabolic wastes. Initially, diabetic nephropathy is manifested as proteinuria, primarily albuminuria. As glomerular changes progress, glomerular filtration becomes progressively impaired, resulting in the development of azotemia and eventually uremia. With severe fibrosis of the glomeruli, oliguric and then anuric renal failure develops. There is no specific treatment for diabetic nephropathy apart from meticulous metabolic control of the diabetic state, conservative medical management of the renal insufficiency, and control of systemic hypertension.

### **Systemic Hypertension**

Diabetes mellitus and hypertension commonly co-exist in dogs. Struble et al. (1998) found the prevalence of hyperten-

sion to be 46% in 50 insulin-treated diabetic dogs, in which hypertension was defined as systolic, diastolic, or mean blood pressure greater than 160, 100, and 120 mm Hg, respectively. The development of hypertension was associated with the duration of diabetes and an increased albumin: creatinine ratio in the urine. Diastolic and mean blood pressure were higher in dogs with longer duration of disease. A correlation between control of glycemia and blood pressure was not identified. Treatment for hypertension should be initiated if the systolic blood pressure is consistently greater than 160 mm Hg.

## **Prognosis**

The prognosis is dependent on the presence and reversibility of concurrent diseases, ease of regulation of the diabetic state with insulin, and client commitment toward treating the disease. The mean survival time in diabetic dogs is approximately 3 years from the time of diagnosis. This survival time is somewhat skewed because dogs are often 8 to 12 years old at the time of diagnosis and a relatively high mortality rate exists during the initial 6 months because of concurrent lifethreatening or uncontrollable disease (e.g., ketoacidosis, acute pancreatitis, renal failure). Diabetic dogs that survive the initial 6 months can easily maintain a good quality of life for longer than 5 years with proper care by the clients, timely evaluations by the veterinarian, and good client-veterinarian communication.

## DIABETES MELLITUS IN CATS

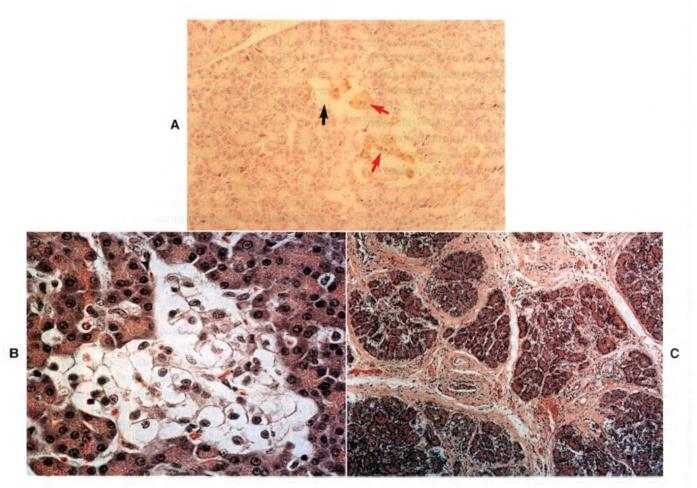
#### Etiology

Common histologic abnormalities in cats with diabetes mellitus include islet-specific amyloidosis,  $\beta$ -cell vacuolation and degeneration, and chronic pancreatitis. The cause of  $\beta$ -cell degeneration is not known. Other diabetic cats have a reduction in the number of pancreatic islets and/or insulincontaining  $\beta$  cells on immunohistochemical evaluation, suggesting additional mechanisms may be involved in the physiopathology of diabetes mellitus in cats. Although lymphocytic infiltration of islets, in conjunction with islet amyloidosis and vacuolation, has been described in diabetic cats, this histologic finding is very uncommon, and  $\beta$  cell and insulin autoantibodies have not been identified in newly diagnosed diabetic cats. The role of genetics remains to be determined.

Noninsulin-dependent type 2 diabetes may be identified in as many as 50% to 70% of newly diagnosed diabetic cats. Islet amyloidosis and insulin resistance are important factors in the development of noninsulin-dependent type 2 diabetes in cats. Islet-amyloid polypeptide (IAPP), or amylin, is the principal constituent of amyloid in adult cats with diabetes, is stored in  $\beta$ -cell secretory granules, and is co-secreted with insulin by the  $\beta$  cell. Stimulants of insulin secretion also stimulate the secretion of amylin. Chronic increased secretion of insulin and amylin, as occurs with obesity and other insulin-resistant states, results in aggregation and deposition

of amylin in the islets as amyloid (Fig. 52-12). IAPP-derived amyloid fibrils are cytotoxic and associated with apoptotic cell death of islet cells. If deposition of amyloid is progressive, as occurs with a sustained demand for insulin secretion in response to persistent insulin resistance, islet cell destruction progresses and eventually leads to diabetes mellitus. The severity of islet amyloidosis and  $\beta$  cell destruction determines, in part, whether the diabetic cat has IDDM or NIDDM. Total destruction of the islets results in IDDM and the need for insulin treatment for the rest of the cat's life. Partial destruction of the islets may or may not result in clinically evident diabetes, insulin treatment may or may not be required to control glycemia, and diabetes may or may not revert to a noninsulin-requiring state once treatment is initiated. If amyloid deposition is progressive, the cat will progress from subclinical diabetes to NIDDM and ultimately to IDDM. Current research regarding the etiopathogenesis of diabetes in the cat suggests that the difference between IDDM and NIDDM is primarily a difference in severity of loss of  $\beta$  cells and severity and reversibility of concurrent insulin resistance. Cats may have IDDM or NIDDM at the time diabetes is diagnosed, cats with NIDDM may progress to IDDM with time, cats with apparent IDDM may revert to a noninsulin requiring state after initiation of treatment, and cats may flip back and forth between IDDM and NIDDM as severity of insulin resistance and impairment of B cell function waxes and wanes.

Approximately 20% of diabetic cats become transiently diabetic, usually within 4 to 6 weeks after the diagnosis of diabetes has been established and treatment has been initiated. In these cats hyperglycemia, glycosuria, and clinical signs of diabetes resolve, and insulin treatment can be discontinued. Some diabetic cats may never require insulin treatment once the initial bout of clinical diabetes mellitus has dissipated, whereas others become permanently insulin dependent weeks to months after the resolution of a prior diabetic state. Studies suggest that cats with transient diabetes mellitus are in a subclinical diabetic state that becomes clinical when the pancreas is stressed by exposure to a concurrent insulin-antagonistic drug or disease, most notably glucocorticoids, megestrol acetate, and chronic pancreatitis (Fig. 52-13). Unlike healthy cats, those with transient diabetes mellitus have a reduced population of  $\beta$  cells, dysfunctional  $\beta$  cells, or both, which impairs the ability of the pancreas to compensate for concurrent insulin resistance. An inadequate insulin response results in hyperglycemia. Persistent hyperglycemia can, in turn, cause hypoinsulinemia by suppressing function of remaining  $\beta$  cells and can induce insulin resistance by promoting downregulation of glucose transport systems and causing a defect in posttransport insulin action. This phenomenon is referred to as glucose toxicity. B cells have an impaired response to stimulation by insulin secretagogues, thereby mimicking IDDM. The effects of glucose toxicity are potentially reversible upon correction of the hyperglycemic state. The clinician makes a correct diagnosis of diabetes mellitus, insulin and treatment of insulin-antagonistic disorders improve hyperglycemia and



#### FIG 52-12

**A,** Severe islet amyloidosis (straight arrow) in a cat with initial noninsulin-dependent diabetes mellitus (NIDDM) that progressed to insulin-dependent diabetes mellitus (IDDM). A pancreatic biopsy specimen was obtained while the animal was in the IDDM state. Residual B cells containing insulin (red arrows) are also present. (Immunoperoxidase stain,  $\times 100$ .) **B,** Severe vacuolar degeneration of islet cells. Pancreatic tissue was evaluated at necropsy 28 months after diabetes was diagnosed and 20 months after cat progressed from NIDDM to IDDM, requiring insulin to control blood glucose concentrations. The cat died from metastatic exocrine pancreatic adenocarcinoma. (H&E,  $\times 500$ .) **C,** Severe chronic pancreatitis with fibrosis in a diabetic cat with IDDM. The cat was euthanized because of persistent problems with lethargy, inappetence, and poorly controlled diabetes mellitus. (H&E,  $\times 100$ .) (**A** from Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

insulin resistance, glucose toxicity and  $\beta$  cell function improve, insulin secretion returns, and an apparent IDDM state resolves. The future requirement for insulin treatment depends on the underlying abnormality in the islets. If the abnormality is progressive (e.g., amyloidosis), eventually enough  $\beta$  cells will be destroyed and IDDM will develop.

#### **Clinical Features**

## **SIGNALMENT**

Although diabetes mellitus may be diagnosed in cats of any age, most diabetic cats are more than 9 years old (mean 10 years) at the time of diagnosis. Diabetes mellitus occurs predominantly in neutered male cats; no apparent breed predis-

position has been discovered, although Burmese cats may be overrepresented in Australia.

#### HISTORY

The history in virtually all diabetic cats includes polydipsia, polyuria, polyphagia, and weight loss. A common complaint of cat owners is the constant need to change the litter and an increase in the size of the litter clumps. Additional clinical signs include lethargy; decreased interaction with family members; lack of grooming behavior and development of a dry, lusterless, unkempt, or matted haircoat; and decreased jumping ability, rear limb weakness, or development of a plantigrade posture (Fig. 52-14). If the client does not notice clinical signs associated with uncomplicated diabetes, a dia-

Inflammation, infection, neoplasia, hormonal disorder or drug causes insulin antagonism

Carbohydrate intolerance and hyperglycemia develop

Glucose toxicity causes apparent IDDM

Insulin treatment and correction (control) of concurrent disorders initiated

Control of hyperglycemia

Resolution of glucose toxicity

\$\beta\$ cells regain function and insulin resistance resolves

Loss of insulin requirements and resolution of IDDM

Cat returns to subclinical diabetic state

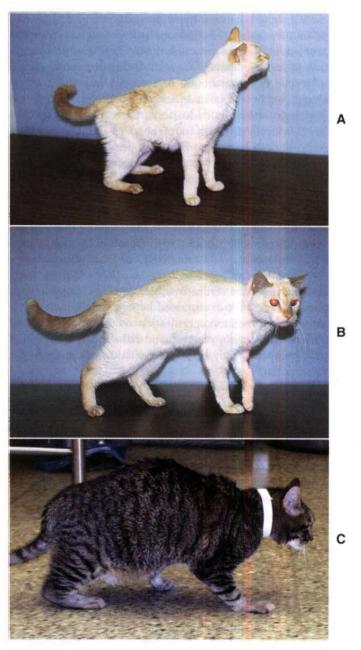
#### FIG 52-13

Sequence of events in the development and resolution of an insulin-requiring diabetic episode in cats with transient diabetes. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

betic cat may be at risk for developing DKA (see p. 796). The time sequence from the onset of initial clinical signs to the development of DKA is unpredictable.

#### PHYSICAL EXAMINATION

Physical examination findings depend on the presence and severity of DKA and the nature of other concurrent disorders. The nonketotic diabetic cat has no classic physical examination findings. Many diabetic cats are obese but otherwise in good physical condition. Cats with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., hyperthyroidism) is present. Newly diagnosed and poorly controlled diabetic cats often stop grooming and develop a dry, lusterless haircoat. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Impaired ability to jump, weakness in the rear limbs, ataxia, or a plantigrade posture (i.e., the hocks touch the ground when the cat walks) may be evident if the cat has developed diabetic neuropathy. Distal muscles of the rear limbs may feel hard on digital palpation, and cats may object to palpation or manipulation of the rear limbs, presumably because of pain associated with the neuropathy. Additional abnor-



#### FIG 52-14

**A,** Plantigrade posture in a cat with diabetes mellitus and exocrine pancreatic insufficiency. **B,** Resolution of hind limb weakness and plantigrade posture after improving glycemic control by adjusting insulin therapy and initiating pancreatic enzyme replacement therapy. **C,** Severe diabetic neuropathy in a cat with diabetes mellitus. Note the palmigrade and plantigrade posture. The more severe and the more chronic the neuropathy, the less likely the neuropathy will improve after improvement in diabetic control.

malities may be identified in the ketoacidotic diabetic cat (see p. 796).

## **Diagnosis**

Establishing the diagnosis of diabetes mellitus is similar for cats and dogs and is based on identification of appropriate

clinical signs, persistent hyperglycemia, and glycosuria (see p. 769). Transient, stress-induced hyperglycemia is a common problem in cats and can cause the blood glucose concentration to increase above 300 mg/dl. Unfortunately, stress is a subjective state that cannot be accurately measured, is not always easily recognized, and may evoke inconsistent responses among individual cats. Glycosuria usually does not develop in cats with transient stress-induced hyperglycemia but can be present if stress is prolonged (i.e., hours). For this reason, presence of appropriate clinical signs, persistent hyperglycemia, and glycosuria should always be documented when establishing a diagnosis of diabetes mellitus in cats. If the clinician is in doubt, the stressed cat can be sent home with instructions for the client to monitor the urine glucose concentration with the cat in the nonstressed home environment. Alternatively, a serum fructosamine concentration can be measured (see p. 774). Documenting an increase in the serum fructosamine concentration supports the presence of sustained hyperglycemia; however, a serum fructosamine concentration in the upper range of normal can occur in symptomatic diabetic cats if the diabetes developed shortly before presentation of the cat to the veterinarian.

Clinical signs develop when hyperglycemia causes glycosuria and are the same regardless of the functional status of pancreatic islets. Information used to establish the diagnosis of diabetes mellitus does not provide information on the status of pancreatic islet health, presence of glucose toxicity, ability of the cat to secrete insulin, or the severity and reversibility of concurrent insulin resistance. Unfortunately, measurements of baseline serum insulin concentration or serum insulin concentrations after administration of an insulin secretagogue have not been consistent aids in differentiating IDDM and NIDDM in the cat. Identification of a baseline serum insulin concentration greater than 15 µU/ml (reference range, 5 to 20 µU/ml) in a newly diagnosed, untreated diabetic cat supports the presence of functional  $\beta$  cells and partial destruction of the islets; however, low or undetectable serum insulin concentrations do not rule out partial \( \beta \) cell loss because of the suppressive effects of glucose toxicity on circulating insulin concentrations.

A thorough evaluation of the cat's overall health is recommended once the diagnosis of diabetes mellitus has been established, for reasons discussed on p. 769. The minimal laboratory evaluation in any diabetic cat should include a CBC, serum biochemical panel, serum thyroxine concentration, and urinalysis with bacterial culture. If available, abdominal ultrasound should also be a routine part of the diagnostic evaluation because of the high prevalence of chronic pancreatitis in diabetic cats. Measurement of baseline serum insulin concentration or performance of an insulin secretory response test is not routinely done in cats because of problems encountered with glucose toxicity. Additional tests may be warranted after obtaining the history, performing the physical examination, or identifying ketoacidosis. See Box 52-4 for a list of potential clinical pathologic abnormalities.

#### **Treatment**

The significant incidence of NIDDM in cats raises interesting questions regarding the need for insulin treatment. Glycemic control can be maintained in some diabetic cats with dietary changes, oral hypoglycemic drugs, control of current diseases, discontinuation of insulin-antagonistic drugs, or a combination of these. The ultimate differentiation between IDDM and NIDDM is usually made retrospectively, after the clinician has had several weeks to assess the response of the cat to therapy and to determine the cat's need for insulin. The initial treatment strategy is based on the severity of clinical signs and physical abnormalities, presence or absence of ketoacidosis, general health of the cat, and client wishes. For most newly diagnosed diabetic cats, treatment includes insulin, adjustments in diet, and correction or control of concurrent insulin resistance.

## INITIAL INSULIN RECOMMENDATIONS FOR DIABETIC CATS

Diabetic cats are notoriously unpredictable in their response to exogenous insulin. No single type of insulin is routinely effective in maintaining control of glycemia, even with twicedaily administration. The initial insulin of choice ultimately is based on personal preferences and experiences. Commonly used insulin preparations for the long-term management of diabetic cats include human recombinant NPH, porcine lente, beef/pork PZI, and the insulin analog glargine (see the section on overview of insulin preparations, p. 769; see Fig. 52-11). All have potential problems in diabetic cats, primarily related to duration of insulin effect, not species of insulin and insulin antibody formation. Although lente and NPH insulin are consistently and rapidly absorbed after subcutaneous administration, the duration of effect of lente and especially NPH insulin can be considerably shorter than 12 hours, resulting in inadequate control of glycemia despite twice-daily administration (see Table 52-2). Although PZI is a longer-acting insulin, the timing of the glucose nadir is variable and occurs within 9 hours of PZI administration in the majority of treated diabetic cats. In one study PZI significantly improved control of glycemia in newly diagnosed diabetic cats and poorly controlled diabetic cats previously treated with ultralente or NPH insulin (Nelson et al., 2001). Comparison of efficacy between PZI and lente insulin has not been reported.

Insulin glargine is the longest-acting commercially available insulin for treatment of diabetes in humans and is currently a popular initial choice by veterinarians for the treatment of diabetes in cats. An unpublished study identified better glycemic control and a higher diabetes remission rate in newly diagnosed diabetic cats treated with glargine twice a day, compared with lente or PZI administered twice a day (Weaver and Rand, 2005). Another study found no difference in glycemic control in diabetic cats treated with glargine once a day versus diabetic cats treated with lente insulin twice a day, and a higher diabetes remission rate in diabetic cats treated with lente insulin (Weaver et al., 2006). In my experience, the duration of effect of glargine is quite

variable, with the glucose nadir occurring as soon as 4 hours and as late as 20 hours after administration. Glargine works well when given once or twice a day in some diabetic cats and does not work very well in others. Problems are usually related to duration of effect (i.e., too short or too long).

Currently, my personal preference for the initial treatment of newly diagnosed diabetes in cats is PZI at an initial dose of 1 U/cat. Because the majority of diabetic cats require PZI insulin twice a day, I prefer to start with twice-daily insulin therapy while the insulin dose is low to prevent problems with hypoglycemia and the Somoygi response. I switch to lente insulin given twice a day if problems with prolonged duration of PZI effect develop and glycemic control cannot be maintained with once-daily PZI, and I switch to glargine given twice a day if problems with short duration of PZI effect develop. When using glargine for the treatment of newly diagnosed diabetic cats, I use an initial dose of 1 unit/ cat administered once a day and switch to twice-daily therapy if subsequent blood glucose evaluations support a duration of effect of 12 hours or less. If PZI insulin becomes unavailable, I would use porcine lente insulin at an initial dose of 1 U/cat twice a day in the newly diagnosed diabetic cat.

#### DIET

The general principles for dietary therapy are listed in Box 52-6. Obesity, feeding practices, and content of the diet warrant discussion in diabetic cats. Obesity is common in diabetic cats and results from excessive caloric intake typically caused by free-choice feeding of dry cat food. Obesity causes reversible insulin resistance that resolves as obesity is corrected. Control of glycemia often improves, and some diabetic cats may revert to a subclinical diabetic state after weight reduction. Correction of obesity is difficult in cats because it requires restriction of daily caloric intake without a corresponding increase in caloric expenditure (i.e., exercise). Although there are several diets specifically formulated for weight reduction in cats, diets containing increased amounts of fiber and diets containing increased protein and decreased carbohydrate should be used in the obese diabetic cat for reasons discussed later. The reader is referred to Chapter 54 for more information on correction of obesity in cats.

The eating habits of cats vary considerably, from those cats that eat everything at the time it is offered to those that graze throughout the day and night. The primary goal of dietary therapy is to minimize the impact of a meal on post-prandial blood glucose concentrations. Consuming the same amount of calories in multiple small amounts throughout a 12-hour period should have less impact than consuming the calories at a single large meal. Half of the cat's total daily caloric intake should be offered at the time of each insulin injection and remain available to the cat to consume when it wishes. Attempts to force a grazing cat to eat the entire meal at one time usually fail and are not warranted as long as the cat has access to the food during the ensuing 12 hours. A similar approach is taken for diabetic dogs that are finicky eaters.

Cats are carnivores and, as such, have higher dietary protein requirements than omnivores such as humans and dogs. Hepatic glucokinase and hexokinase activity is lower in cats, compared with that for carnivores with omnivorous eating habits, and suggests that diabetic cats may be predisposed to developing higher postprandial blood glucose concentrations after consumption of diets containing a high carbohydrate load, and vice versa. Dietary studies in diabetic cats have documented improved control of glycemia with diets containing increased fiber content, increased protein and decreased carbohydrate content, and increased fat and decreased carbohydrate content plus treatment with the α-glucosidase inhibitor acarbose. The central theme in these dietary studies has been restriction of carbohydrate absorption by the gastrointestinal tract, either by inhibiting starch digestion (acarbose), inhibiting intestinal glucose absorption (fiber), or decreasing carbohydrate ingestion (low carbohydrate-containing diets). Intuitively, the most effective means to minimize gastrointestinal absorption of carbohydrates in the diabetic cat is to feed diets that contain minimal amounts of carbohydrate. Current recommendations include diets with high protein and low carbohydrate content and diets containing increased fiber and moderate carbohydrate content (see Box 52-6). Which diet will be most beneficial in improving control of glycemia in any given diabetic cat is unpredictable. The initial diet of choice is based on personal preference. Currently, I initially use diets containing high protein and low carbohydrate content, and if palatability, problems with renal insufficiency, or adverse effects become an issue or poor control of glycemia persists despite adjustments in insulin therapy, a switch to one of the fibercontaining diets should be considered. Diets containing high fat and low carbohydrate content (e.g., growth diets) are not recommended because of concerns related to the impact of high dietary fat content on obesity, hepatic lipidosis, chronic pancreatitis, and insulin resistance—the latter induced by increased circulating concentrations of nonesterified fatty acids,  $\beta$ -hydroxybutyric acid, and triglycerides.

## IDENTIFICATION AND CONTROL OF CONCURRENT PROBLEMS

Identification and correction of concurrent disorders that cause insulin resistance and interfere with the success of insulin therapy is critical to the successful treatment of diabetes in cats. Examples include obesity; chronic pancreatitis and other chronic inflammatory diseases; infection; and insulin-resistant disease such as hyperthyroidism, hyperadrenocorticism, and acromegaly. In diabetic cats with partial loss of  $\beta$  cells correction of insulin resistance may result in reversion from an insulin-dependent to a non-insulindependent or subclinical diabetic state. An evaluation of the diabetic cat for concurrent problems is indicated at the time diabetes is diagnosed and whenever control of glycemia deteriorates in a previously well-controlled cat and should include a thorough history, physical examination, CBC, serum biochemistry panel, serum thyroxine concentration, urinalysis with culture, and (if available) abdominal ultrasound.

### **ORAL HYPOGLYCEMIC DRUGS**

In the United States, five classes of oral hypoglycemic drugs are approved for the treatment of NIDDM in human beings: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and α-glucosidase inhibitors. These drugs work by stimulating pancreatic insulin secretion (sulfonylureas, meglitinides), enhancing tissue sensitivity to insulin (biguanides, thiazolidinediones), or slowing postprandial intestinal glucose absorption (α-glucosidase inhibitors). Although controversial, chromium and vanadium are trace minerals that may also function as insulin sensitizers. Studies have documented the efficacy of sulfonylureas for treating diabetes in cats and α-glucosidase inhibitors for improving glycemic control in diabetic dogs. Insulin sensitizers as the sole therapeutic agent are of questionable benefit in diabetic dogs and cats because they require the presence of circulating insulin to be effective. Most diabetic cats subsequently shown to have NIDDM have low or nondetectable insulin concentrations at the time diabetes is diagnosed, in part because of the effects of concurrent glucose toxicity on circulating insulin concentrations.

### Sulfonylureas

Sulfonylurea drugs (e.g., glipizide, glyburide) are the most commonly used oral hypoglycemic drugs for the treatment of diabetes mellitus in cats. Sulfonylureas stimulate insulin secretion by pancreatic  $\beta$  cells. Some endogenous pancreatic insulin secretory capacity must exist for sulfonylureas to be effective. Clinical response to glipizide and glyburide treatment in diabetic cats has been variable, ranging from excellent (i.e., blood glucose concentrations decreasing to less than 200 mg/dl) to partial response (i.e., clinical improvement but failure to resolve hyperglycemia) to no response. Presumably, the population of functioning B cells varies from none (severe IDDM) to near normal (mild NIDDM) in treated cats, resulting in a response range from none to excellent. Cats with a partial response to glipizide have some functioning  $\beta$  cells but not enough to decrease the blood glucose concentration to less than 200 mg/dl. These cats may have severe NIDDM or the early stages of IDDM. Glipizide treatment has been found effective in improving clinical signs and severity of hyperglycemia in approximately 20% of diabetic cats.

No consistent parameters have been identified that allow the clinician to prospectively determine which cats will respond to glipizide or glyburide therapy. Identifying a high preprandial serum insulin concentration or an increase in serum insulin concentration during an insulin secretagogue test supports the diagnosis of NIDDM, but failure to identify these changes does not rule out the potential for a beneficial response to glipizide or glyburide. Selection of diabetic cats for treatment with glipizide must rely heavily on the veterinarian's assessment of the cat's health, severity of clinical signs, presence or absence of ketoacidosis, other diabetic complications (e.g., peripheral neuropathy), and the client's desires.

Glipizide (Glucotrol, Pfizer; 2.5 mg/cat administered q12h) and glyburide (Micronase, Pharmacia and Upjohn Company; 0.625 mg/cat q12h) are initially administered in conjunction with a meal to diabetic cats that are nonketotic and relatively healthy on physical examination (Fig. 52-15). Each cat is examined weekly during the first month of therapy. A history, complete physical examination, body weight, urine glucose/ ketone measurement, and blood glucose concentration are evaluated at each examination. If adverse reactions (Table 52-4) have not occurred after 2 weeks of treatment, the glipizide and glyburide dose is increased to 5.0 mg and 1.25 mg, respectively, q12h. Therapy is continued as long as the cat is stable. If euglycemia or hypoglycemia develops, the dose may be tapered down or discontinued and blood glucose concentrations reevaluated 1 week later to assess the need for the drug. If hyperglycemia recurs, the dose is increased or the sulfonylurea is reinitiated, with a reduction in dose in those cats previously developing hypoglycemia. Sulfonylurea treatment is discontinued and insulin therapy initiated if clinical signs continue to worsen, the cat becomes ill or develops ketoacidosis or peripheral neuropathy, blood glucose concentrations remain greater



**TABLE 52-4** 

Adverse Reactions to Glipizide Treatment in Diabetic Cats

ADVERSE REACTION	RECOMMENDATION
Vomiting within 1 hour of administration	Vomiting usually subsides after 2 to 5 days of glipizide therapy; decrease dose or frequency of administration if vomiting is severe; discontinue if vomiting persists >1 week
Increased serum hepatic enzyme activities	Continue treatment and monitor enzymes every 1 to 2 weeks initially; discontinue glipizide if cat becomes ill (lethargy, inappetence, vomiting) or the alanine transaminase activity exceeds 500 IU/L
Icterus	Discontinue glipizide treatment; reinstitute glipizide treatment at lower dose and frequency of administration once icterus resolves (usually within 2 weeks); discontinue treatment permanently if icterus recurs
Hypoglycemia	Discontinue glipizide treatment; recheck blood glucose concentration in 1 week; reinstitute glipizide therapy at lower dose or frequency of administration if hyperglycemia recurs

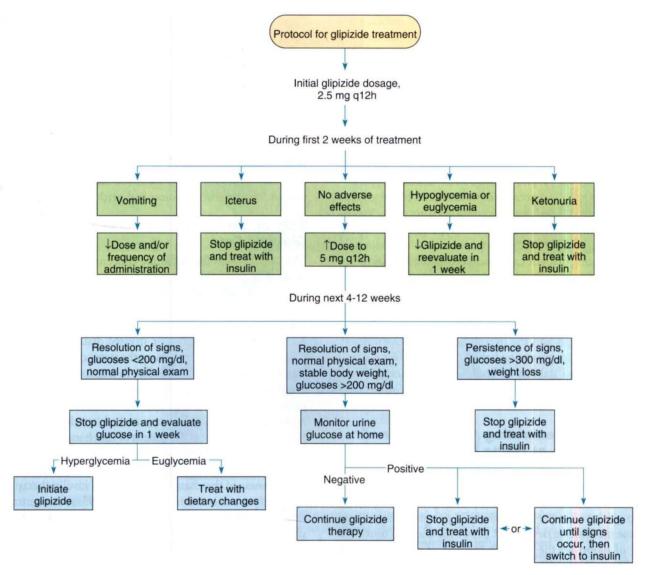


FIG 52-15
Algorithm for treating diabetic cats with the oral sulfonylurea drug, glipizide. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

than 300 mg/dl after 1 to 2 months of therapy, or the client becomes dissatisfied with the treatment. In some cats sulfonylureas become ineffective weeks to months later, and exogenous insulin is ultimately required to control the diabetic state. Presumably, the progression to IDDM coincides with progressive loss of  $\beta$  cells, a loss that may be exacerbated by sulfonylurea treatment. Regardless, the primary value of sulfonylureas is an alternative palatable option (pills versus injections) for clients initially unwilling to consider insulin injections and contemplating euthanasia of their cat. During the ensuing weeks many of these clients become willing to try insulin injections if sulfonylurea therapy fails.

#### Acarbose

Although the **u**-glucosidase inhibitor acarbose has been effective in improving glycemic control in diabetic dogs and

cats, the drug is not commonly used because of cost and adverse effects. Diarrhea and weight loss as a result of carbohydrate malassimilation occur in approximately 35% of treated dogs. Feeding carbohydrate-restricted diets is recommended in lieu of acarbose treatment in diabetic cats.

## IDENTIFYING INITIAL INSULIN REQUIREMENTS

The approaches to identifying insulin requirements in the newly diagnosed diabetic cat and dog are similar and discussed on p. 773. Most clients of diabetic cats are happy with the response to insulin treatment if the blood glucose concentrations range between 100 and 300 mg/dl throughout the day. Diabetic cats can have problems with hypoglycemia and the Somogyi response (see p. 780) at relatively small doses of insulin (1 to 2 U/injection). As such, the preference

is to have the client administer a fixed dose of insulin once control of glycemia is attained and discourage clients from adjusting the insulin dose at home without first consulting their veterinarian.

## **Techniques for Monitoring Diabetic Control**

The techniques for monitoring diabetic control are discussed on p. 774. One important factor that affects monitoring of diabetic cats is the propensity to develop stress-induced hyperglycemia caused by frequent visits to the veterinary hospital for blood samplings. Once stress-induced hyperglycemia develops, it is a perpetual problem and blood glucose measurements can no longer be considered accurate. Veterinarians must remain wary of stress hyperglycemia in diabetic cats and should take steps to prevent its development. Micromanaging diabetic cats is not recommended, and serial blood glucose curves should be done only when the clinician perceives a need to change insulin therapy. The determination of good versus poor control of glycemia should be based on the client's subjective opinion of the presence and severity of clinical signs and the overall health of the pet, ability of the cat to jump, grooming behavior, findings on physical examination, and stability of body weight. Generation of a serial blood glucose curve should be reserved for newly diagnosed and poorly controlled diabetic cats.

## Protocol for Generating the Serial Blood Glucose Curve at Home

An alternative to hospital-generated blood glucose curves is to have the client generate the blood glucose curve at home using the marginal ear vein prick technique in cats (the ear or lip prick technique in dogs) and a portable home blood glucose monitoring device that allows the client to touch the drop of blood on the ear with the end of the glucose test strip (Fig. 52-16). The marginal ear vein prick technique decreases the need for physical restraint during sample collection, thereby minimizing the cat's discomfort and stress. Accuracy of blood glucose results are similar when blood for glucose determination is obtained by ear prick and venipuncture. However, blood glucose results obtained by portable blood glucose monitoring devices may overestimate or, more commonly, underestimate the actual blood glucose values obtained with reference methods. This inherent error must be considered when interpreting blood glucose results obtained by a portable home blood glucose monitoring device. Several Web sites explain in detail the marginal ear vein prick technique in layman's terms and provide information on client experiences with the technique and with different portable home blood glucose meters. After diagnosing diabetes, the clinician should recommend a particular Web site and find out whether the client would be interested in monitoring blood glucose concentrations at home. The clinician should allow for ample time to teach the technique to clients who are willing to give it a try and provide advice regarding the proper way to perform a blood glucose curve (ideally, no more frequently than 1 day every 4 weeks) and how often to measure the blood glucose concentration on

the day of the curve (typically, at the time of insulin administration and 3, 6, 9, and 12 hours later). Use of the ear prick technique in cats has produced excellent results. Stress is often significantly reduced, and accuracy of the blood glucose measurements improved. Problems with the marginal ear vein prick technique include overzealous clients who start monitoring blood glucose concentrations too frequently, insulin overdosing and the Somogyi response caused by clients who interpret blood glucose results and adjust the insulin dose independent of input from the veterinarian, difficulty obtaining blood from the ear vein, and cats who do not tolerate manipulation and pricking of the ear.

## Role of Serum Fructosamine in Stressed Diabetic Cats

The use of serum fructosamine concentrations for assessing control of glycemia is discussed on p. 777. Serum fructosamine concentrations are not affected by acute transient increases in blood glucose concentration. Unlike blood glucose measurements, evaluation of serum fructosamine concentration in fractious or stressed diabetic cats provides reliable objective information on the status of glycemic control during the previous 2 to 3 weeks. In fractious or stressed cats the clinician must make an educated guess as to where the problem lies (e.g., wrong type of insulin, low insulin dose), make an adjustment in therapy, and rely on changes in serum fructosamine to assess the benefit of the change in treatment. Serum fructosamine concentrations can be measured before and 2 to 3 weeks after changing insulin therapy to assess the effectiveness of the change. If changes in insulin therapy are appropriate, a decrease in serum fructosamine concentration should occur. If the serum fructosamine concentration is the same or has increased, the change was ineffective in improving glycemic control, another change in therapy based on an educated guess should be done, and the serum fructosamine measured again 2 to 3 weeks later.

#### INSULIN THERAPY DURING SURGERY

The approaches to managing the diabetic cat and dog during surgery are similar and are discussed on p. 778.

#### COMPLICATIONS OF INSULIN THERAPY

Complications of insulin therapy are similar for diabetic dogs and cats and are discussed on p. 779. The most common complications of insulin therapy in the diabetic cat are recurring hypoglycemia; insulin overdose, which causes the Somogyi response; incorrect assessment of glycemic control caused by stress-induced hyperglycemia; short duration of effect of NPH; lente and, less commonly, PZI and glargine insulin; prolonged duration of effect of PZI and glargine insulin; and insulin resistance caused by concurrent inflammatory and hormonal disorders, most notably chronic pancreatitis.

## Stress Hyperglycemia

Transient hyperglycemia is a well-recognized problem in fractious, scared, or otherwise stressed cats. Hyperglycemia



#### FIG 52-16

Ear prick technique for measuring blood glucose concentration. **A,** A hot washcloth is applied to the pinna for 2 to 3 minutes to increase circulation to the ear. **B,** A spot is identified on the periphery of the outer side of the pinna, a small coating of petrolatum jelly is applied, and the spot is pricked with the lancet device supplied with the portable blood glucose meter. Gauze should be placed between the pinna and the digit holding the pinna to prevent pricking the finger if the blade of the lancet accidentally passes through the pinna. Petrolatum jelly is applied to help the blood form into a ball on the pinna as it seeps from the site that is lanced. **C,** Digital pressure is applied in the area of the lanced skin to promote bleeding. The glucose test strip is touched to the drop of capillary blood that forms and is removed once enough blood has been drawn into the test strip to activate the meter.

develops as a result of increased catecholamines and, in struggling cats, lactate concentrations. Blood glucose concentrations typically exceed 200 mg/dl in affected cats, and values in excess of 300 mg/dl are common. Stress hyperglycemia can significantly increase blood glucose concentrations in diabetic cats despite the administration of insulin, an effect that seriously compromises the clinician's ability to accurately judge the effectiveness of the insulin injection. Frequent hospitalizations and venipunctures for monitoring blood glucose concentrations are the most common cause of stress hyperglycemia. Blood glucose concentrations can remain greater than 400 mg/dl throughout the day despite administration of insulin. Failure to recognize the effect of stress on blood glucose results may lead to the erroneous perception that the diabetic cat is poorly controlled. Insulin

therapy is invariably adjusted, often by increasing the insulin dose, and another blood glucose curve recommended 1 to 2 weeks later. A vicious cycle ensues, which eventually culminates in the Somogyi response, clinically apparent hypoglycemia, or referral for evaluation of insulin resistance.

Failure to identify the presence of stress hyperglycemia and its impact on the interpretation of blood glucose measurements is one of the most important reasons that the status of glycemic control in diabetic cats is misinterpreted. Stress hyperglycemia should be suspected if the cat is visibly upset or aggressive or struggles during restraint and the venipuncture process. However, stress hyperglycemia can also be present in diabetic cats that are easily removed from the cage and do not resist the blood-sampling procedure. These cats are scared, but rather than become aggressive, they remain

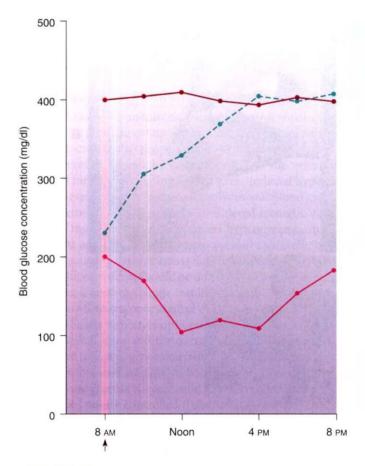


FIG 52-17

Blood glucose concentration curves in a 5.3-kg male cat receiving 2 U of recombinant human ultralente insulin (pink line) 2 weeks after the initiation of insulin therapy, 2 U of recombinant human ultralente insulin (blue line) 2 months later, and 6 U of recombinant human ultralente insulin Ired line) 4 months later. The insulin dose had been gradually increased on the basis of the blood glucose concentration curves. The client reported minimal clinical signs regardless of the insulin dose; at the 4-month recheck the cat had maintained its body weight and results of the physical exanination were normal. The cat became progressively more fractious during each hospitalization, supporting the existence of stress-induced hyperglycemia as the reason for the discrepancy between the blood glucose values and other parameters used to evaluate glycemic control. ↑, Subcutaneous insulin injection and food. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

crouched in the back of the cage, often have dilated pupils, and usually are flaccid when handled. Stress hyperglycemia should also be suspected if a disparity exists between assessment of glycemic control based on results of the history, physical examination, and stability of body weight; assessment of glycemic control based on results of blood glucose measurements; or when the initial blood glucose concentration measured in the morning is in an acceptable range (i.e., 150 to 250 mg/dl) but subsequent blood glucose concentrations increase steadily throughout the day (Fig. 52-17). Once stress hyperglycemia develops, it is a perpetual problem and

blood glucose measurements can no longer be considered accurate. If stress hyperglycemia is suspected, reliance on home monitoring of blood glucose or evaluation of sequential serum fructosamine concentrations (see p. 792) should be done, in addition to the history and physical examination findings.

## Hypoglycemia

Hypoglycemia, a common complication of insulin therapy, is discussed on p. 779. In diabetic cats symptomatic hypoglycemia is most apt to occur after sudden large increases in the insulin dose, after sudden improvement in concurrent insulin resistance, with excessive duration of insulin action in cats receiving insulin twice a day, after prolonged inappetence, and in insulin-treated cats that have reverted to a non-insulin-dependent state. In these situations severe hypoglycemia may occur before glucose counterregulation (i.e., secretion of glucagon, cortisol, epinephrine, growth hormone) is able to compensate for and reverse low blood glucose concentrations. The initial treatment approach for hypoglycemia is to discontinue insulin until hyperglycemia recurs and then reduce the ensuing insulin dose 25% to 50%. If hypoglycemia remains a reoccurring problem despite reductions in the insulin dose, excessive duration of insulin effect (see p. 781) or reversion to a noninsulin-dependent diabetic state should be considered. Reversion to a noninsulin-dependent diabetic state should be suspected if hypoglycemia remains a persistent problem despite administration of small doses of insulin (i.e., 1 U or less per injection) and administration of insulin once a day, if blood glucose concentrations are consistently below 150 mg/dl before insulin administration, if serum fructosamine concentration is less than 350 µmol/L, or if urine glucose test strips are consistently negative. Insulin therapy should be discontinued and periodic urine glucose testing should be performed in the home environment to identify recurrence of glycosuria.

## Insulin Overdosing and the Somogyi Response

Insulin overdosing and the Somogyi response is discussed on p. 780. A similar phenomenon, characterized by wide fluctuations in blood glucose concentration after which there are several days of persistent hyperglycemia, is recognized clinically in diabetic cats. However, the exact role of the counterregulatory hormones remains to be clarified. Insulin overdose that induces the Somogyi response is one of the most common causes of poor glycemic control in diabetic cats. It can be induced with insulin doses of 1 to 2 U per injection and can result in cats receiving 10 to 15 U of insulin per injection as veterinarians react to the persistence of clinical signs and increased blood glucose and serum fructosamine concentrations. A cyclic history of 1 or 2 days of good glycemic control after which there are several days of poor control should raise suspicion for insulin overdosing and the Somogyi response. Arbitrarily decreasing the insulin dose and evaluating the clinical response over the

ensuing 2 to 5 days is perhaps the best way to establish the diagnosis.

## Insulin Underdosing

Insulin underdosing is discussed on p. 780. Control of glycemia can be established in most diabetic cats using 1 U or less of insulin/kg of body weight administered twice each day. In general, insulin underdosing should be considered if the insulin dose is less than 1 U/kg/injection and the cat is receiving insulin twice a day. If insulin underdosing is suspected, the dose of insulin should be gradually increased by 0.5 to 1 U/injection per week. The effectiveness of the change in therapy should be evaluated by client perception of clinical response and measurement of serum fructosamine or serial blood glucose concentrations. Other causes for poor glycemic control should be ruled out before an increase in the insulin dose above 1 U/kg/injection is considered.

#### Short Duration of Insulin Effect

Short duration of insulin effect is discussed on p. 781. Short duration of insulin effect is a common problem in diabetic cats despite twice-daily insulin administration. Short duration of effect is most common with NPH and lente insulin (see Table 52-2). A diagnosis of short duration of insulin effect is made by demonstrating an initial blood glucose concentration greater than 300 mg/dl combined with a glucose nadir above 80 mg/dl that occurs less than 8 hours after insulin administration and recurrence of hyperglycemia (greater than 250 mg/dl) within 10 hours of the insulin injection (see Fig. 52-7). Treatment involves changing to a longeracting insulin preparation (i.e., PZI or glargine insulin).

## Prolonged Duration of Insulin Effect

Prolonged duration of insulin effect is discussed on p. 781. In diabetic cats problems with prolonged duration of insulin effect are most common with twice-daily administration of PZI and glargine insulin.

### Inadequate Insulin Absorption

Slow or inadequate absorption of subcutaneously deposited insulin was most commonly observed in diabetic cats receiving ultralente insulin, a long-acting basal insulin that had a slow onset and prolonged duration of effect. In affected cats the blood glucose concentration would decrease minimally, if at all, despite insulin doses of 8 to 12 U/cat. Ultralente insulin is no longer commercially available. A similar problem has not been reported for PZI or glargine insulin. Impaired and erratic absorption of insulin may occur as a result of thickening of the skin and inflammation of the subcutaneous tissues caused by chronic injection of insulin in the same area of the body. Rotation of the injection site helps prevent this problem.

## **Circulating Insulin-Binding Antibodies**

Insulin-binding antibodies are discussed on p. 782. Feline and beef insulin are similar, and feline, human, and porcine insulin differ. Fortunately, insulin antibody formation is not

common in diabetic cats treated with exogenous human insulin, despite differences between human and feline insulin. Studies identified an approximately equal frequency of positive serum insulin antibody titers in diabetic cats treated with beef insulin and recombinant human insulin. In my experience, antiinsulin antibody titers are weakly positive in most cats that develop insulin antibodies, prevalence of persistent titers is low, and presence of serum insulin antibodies do not appear to affect control of glycemia. Insulin resistance caused by insulin antibody formation appears to be uncommon. Switching from recombinant human or porcine source insulin to beef-/pork-source PZI may improve control of glycemia if insulin antibodies are the suspected cause for insulin ineffectiveness.

## Concurrent Disorders Causing Insulin Resistance

Concurrent disorders causing insulin resistance is discussed on p. 783. The most common concurrent disorders interfering with insulin effectiveness in cats include severe obesity, chronic inflammation such as chronic pancreatitis and gingivitis, renal insufficiency, hyperthyroidism, acromegaly, and hyperadrenocorticism (see Box 52-7). Obtaining a complete history and performing a thorough physical examination are the most important steps in identifying these concurrent disorders. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum thyroxine concentration, urinalysis with bacterial culture, and (if available) abdominal ultrasound should be obtained to further screen for concurrent illness. Additional tests will depend on the results of the initial screening tests (see Box 52-8).

## CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Chronic complications of diabetes mellitus are discussed on p. 783. The most common complications in the diabetic cat are hypoglycemia; chronic pancreatitis; weight loss; poor grooming behavior causing a dry, lusterless, and unkempt haircoat; and peripheral neuropathy of the hind limbs, causing weakness, inability to jump, a plantigrade stance, and ataxia (see Box 52-5). Diabetic cats are also at risk for ketoacidosis.

## **Diabetic Neuropathy**

Diabetic neuropathy is one of the most common chronic complications of diabetes in cats, with a prevalence of approximately 10%. Clinical signs of a co-existent neuropathy in the diabetic cat include weakness, impaired ability to jump, knuckling, a plantigrade posture with the cat's hocks touching the ground when it walks (see Fig. 52-14), muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. Clinical signs may progress to include the thoracic limbs (palmigrade posture; see Fig 52-14). Abnormalities on electrophysiologic testing are consistent with demyelination at all levels of the motor and sensory peripheral nerves and include decreased motor and sensory nerve

conduction velocities in pelvic and thoracic limbs and decreased muscle action potential amplitudes. Electromyographic abnormalities are usually absent and, when identified, are consistent with denervation. The most striking abnormality detected on histologic examination of nerve biopsies from affected cats is Schwann cell injury; axonal degeneration is identified in severely affected cats. The cause of diabetic neuropathy is not known. Currently, there is no specific therapy. Aggressive glucoregulation with insulin may improve nerve conduction and reverse the posterior weakness and plantigrade posture (see Fig. 52-14). However, the response to therapy is variable, and the risks of hypoglycemia increase with aggressive insulin treatment. Generally, the longer the neuropathy has been present and the more severe the neuropathy, the less likely it is that improving glycemic control will reverse the clinical signs of neuropathy.

### **Prognosis**

Diabetic cats and dogs have a similar prognosis (see p. 785). The mean survival time in diabetic cats is approximately 3 years from time of diagnosis. However, this survival time is skewed because cats are usually 8 to 12 years old at the time of diagnosis, and a high mortality rate exists during the first 6 months because of concurrent life-threatening or uncontrollable disease (e.g., ketoacidosis, pancreatitis, renal failure). Diabetic cats that survive the first 6 months can easily live longer than 5 years with the disease.

## DIABETIC KETOACIDOSIS

### Etiology

The etiopathogenesis of DKA is complex and usually affected by concurrent clinical disorders. Virtually all dogs and cats with DKA have a relative or absolute deficiency of insulin. DKA develops in some diabetic dogs and cats even though they receive daily injections of insulin, and their circulating insulin concentrations may even be increased. The "relative" insulin deficiency in these animals is created by concurrent insulin resistance, which in turn is created by concurrent disorders such as pancreatitis, infection, or renal insufficiency. Increased circulating concentrations of diabetogenic hormones, most notably glucagon, accentuate insulin deficiency by promoting insulin resistance; stimulate lipolysis, leading to ketogenesis; and stimulate hepatic gluconeogenesis, which worsens hyperglycemia.

Insulin deficiency and insulin resistance, together with increased circulating concentrations of diabetogenic hormones, play a critical role in the stimulation of ketogenesis. For the synthesis of ketone bodies (i.e., acetoacetic acid,  $\beta$ -hydroxybutyric acid, acetone) to be enhanced, there must be two major alterations in intermediary metabolism; (1) enhanced mobilization of free fatty acids (FFAs) from triglycerides stored in adipose tissue and (2) a shift in hepatic metabolism from fat synthesis to fat oxidation and ketogenesis. Insulin is a powerful inhibitor of lipolysis and FFA oxidation. A relative or absolute deficiency of insulin allows

lipolysis to increase, thus increasing the availability of FFAs to the liver and in turn promoting ketogenesis. As ketones continue to accumulate in the blood, the body's buffering system becomes overwhelmed and metabolic acidosis develops. As ketones accumulate in the extracellular space, the amount eventually surpasses the renal tubular threshold for complete resorption and they spill into the urine, contributing to the osmotic diuresis caused by glycosuria and enhancing the excretion of solutes (e.g., sodium, potassium, magnesium). Insulin deficiency per se also contributes to the excessive renal losses of water and electrolytes. The result is an excessive loss of electrolytes and water, leading to volume contraction, an underperfusion of tissues, and the development of prerenal azotemia. The rise in the blood glucose concentration raises plasma osmolality, and the resulting osmotic diuresis further aggravates the rise in plasma osmolality by causing water losses in excess of salt loss. The increase in plasma osmolality causes water to shift out of cells, leading to cellular dehydration. The metabolic consequences of DKA, which include severe acidosis, hyperosmolality, obligatory osmotic diuresis, dehydration, and electrolyte derangements, eventually become life threatening.

#### **Clinical Features**

DKA is a serious complication of diabetes mellitus that occurs most commonly in dogs and cats with diabetes that has gone undiagnosed. Less commonly, DKA develops in an insulin-treated diabetic dog or cat that is receiving an inadequate dose of insulin, often occurring in conjunction with an infectious, inflammatory, or insulin-resistant hormonal disorder. Because of the close association between DKA and newly diagnosed diabetes mellitus, the signalment of DKA in dogs and cats is similar to that of nonketotic diabetics.

The history and physical examination findings are variable, in part because of the progressive nature of the disorder and the variable time between the onset of DKA and client recognition of a problem. Polyuria, polydipsia, polyphagia, and weight loss develop initially but are either unnoticed or considered insignificant by the client. Systemic signs of illness (e.g., lethargy, anorexia, vomiting) ensue as ketonemia and metabolic acidosis develop and worsen, with the severity of these signs directly related to the severity of the metabolic acidosis and the nature of concurrent disorders that are often present. The time interval from the onset of the initial clinical signs of diabetes to the development of systemic signs of DKA is unpredictable and ranges from a few days to longer than 6 months. Once ketoacidosis begins to develop, however, severe illness usually becomes evident within 7 days.

Common physical examination findings include dehydration, lethargy, weakness, tachypnea, vomiting, and sometimes a strong odor of acetone on the breath. Slow, deep breathing may be observed in animals with severe metabolic acidosis. Gastrointestinal tract signs such as vomiting and abdominal pain are common in animals with DKA, in part because of the common concurrent occurrence of pancreatitis. Other intraabdominal disorders should also be con-

sidered and diagnostic tests (e.g., abdominal ultrasound) performed to help identify the cause of the gastrointestinal signs.

### Diagnosis

The diagnosis of diabetes mellitus is based on appropriate clinical signs, persistent fasting hyperglycemia, and glycosuria. Documenting ketonuria with reagent test strips that measure acetoacetic acid (KetoDiastix; Ames Division, Miles Laboratories) establishes the diagnosis of diabetic ketosis (DK), and documenting metabolic acidosis establishes the diagnosis of DKA. If ketonuria is not present but DKA is suspected, serum or urine can be tested for acetone using Acetest tablets (Ames Division, Miles Laboratories), serum can be tested for the presence of  $\beta$ -hydroxybutyrate using a benchtop chemistry analyzer, and plasma from heparinized hematocrit tubes can be used to test for the presence of acetoacetic acid using urine reagent strips used to document ketonuria, β-hydroxybutyrate and acetone are derived from acetoacetic acid, and commonly used urine reagent strips do not detect β-hydroxybutyrate and acetone. However, it is extremely uncommon for DKA to develop without an excess of acetoacetic acid.

## Treatment of "Healthy" Dogs or Cats with Diabetic Ketosis or Diabetic Ketoacidosis

If systemic signs of illness are absent or mild, serious abnormalities are not readily identifiable on physical examination, and metabolic acidosis is mild (i.e., total venous CO2 or arterial bicarbonate concentration greater than 16 mEq/L), short-acting regular crystalline insulin can be administered subcutaneously three times daily until the ketonuria resolves. Fluid therapy and intensive care are usually not needed. The insulin dose should be adjusted on the basis of blood glucose concentrations. To minimize hypoglycemia, the dog or cat should be fed one third of its daily caloric intake at the time of each insulin injection. The blood glucose and urine ketone concentrations, as well as the animal's clinical status, should be monitored. A decrease in the blood glucose concentration implies a decrease in ketone production. This, in combination with metabolism of ketones and loss of ketones in urine, will usually correct ketosis within 48 to 96 hours of initiating insulin therapy. Prolonged ketonuria is suggestive of a significant concurrent illness or inadequate blood insulin concentrations to suppress lipolysis and ketogenesis. Once the ketosis has resolved and the dog or cat is stable, eating, and drinking, insulin therapy may be initiated using longeracting insulin preparations (see pp. 765 and 788).

## Treatment of Sick Dogs or Cats with Diabetic Ketoacidosis

Aggressive therapy is called for if the dog or cat has systemic signs of illness (e.g., lethargy, anorexia, vomiting); physical examination reveals dehydration, depression, weakness, or a combination of these; or metabolic acidosis is severe (i.e., total venous CO<sub>2</sub> or arterial bicarbonate concentration less than 12 mEq/L). The five goals of treatment of a severely ill

ketoacidotic, diabetic pet are (1) to provide adequate amounts of insulin to suppress lipolysis, ketogenesis, and hepatic gluconeogenesis; (2) to restore water and electrolyte losses; (3) to correct acidosis; (4) to identify the factors precipitating the present illness; and (5) to provide a carbohydrate substrate (i.e., dextrose) when necessary to allow continued administration of insulin without causing hypoglycemia (Box 52-9). Proper therapy does not mean forcing a return to a normal state as rapidly as possible. Because osmotic and biochemical problems can arise as a result of overly aggressive therapy as well as from the disease itself, rapid changes in various vital parameters can be as harmful as, or more harmful than, no change. If all abnormal parameters can be slowly returned toward normal over a period of 24 to 48 hours, therapy is more likely to be successful.

Critically important information for formulating the initial treatment protocol include hematocrit and total plasma protein concentration; serum glucose, albumin, creatinine, and urea nitrogen concentrations; serum electrolytes; venous total CO<sub>2</sub> or arterial acid-base evaluation; and urine specific gravity. Abnormalities frequently associated with DKA are listed in Box 52-10. Once treatment for DKA is initiated, additional studies, such as a CBC, serum biochemistry panel, urinalysis, thoracic radiographs, and abdominal ultrasound, or diagnostic tests for pancreatitis, diestrus in the female dog, hyperthyroidism, and hyperadrenocorticism are usually warranted to identify underlying concurrent disorders (see Box 52-8).

#### **FLUID THERAPY**

Initiation of appropriate fluid therapy should be the first step in the treatment of DKA. Replacement of fluid deficiencies and maintenance of normal fluid balance are important to ensure adequate cardiac output, blood pressure, and blood flow to all tissues. Improvement of renal blood flow is especially critical. In addition to the general beneficial aspects of fluid therapy in any dehydrated animal, fluid therapy can correct the deficiency in total body sodium and potassium, dampen the potassium-lowering effect of insulin treatment, and lower the blood glucose concentration in diabetics, even in the absence of insulin administration. Unfortunately, fluid therapy alone does not suppress ketogenesis. For this reason, insulin is always required.

The type of parenteral fluid initially used will depend on the animal's electrolyte status, blood glucose concentration, and osmolality. Most dogs and cats with DKA have severe deficits in total body sodium, regardless of the measured serum concentration. Unless serum electrolyte concentrations dictate otherwise, the initial IV fluid of choice is 0.9% sodium chloride with appropriate potassium supplementation (see Table 55-1 and Table 55-2). Most dogs and cats with severe DKA usually are sodium depleted and therefore not suffering from dramatic hyperosmolality. Additional replacement crystalloid solutions that could be used if physiologic (0.9%) saline was not available include Ringer's solution, Ringer's lactated solution, Plasma-Lyte 148® (Baxter Healthcare Corporation), and Normosol-R (Abbott Laboratories).



BOX 52-9

### Initial Management of Dogs or Cats with Severe Diabetic Ketoacidosis

#### Fluid Therapy

Type: 0.9% saline

Rate: 60 to 100 ml/kg q24h initially; adjust based on hydration status, urine output, persistence of fluid losses

**Potassium supplement:** based on serum K<sup>+</sup> concentration (Table 55-1); if unknown, initially add KCl to provide 40 mEq of KCl per liter of fluids

**Phosphate supplement:** not indicated until serum phosphorus is less than 1.5 mg/dl, then 0.01 to 0.03 mmol phosphate/kg/hr in calcium-free intravenous fluids

**Dextrose supplement:** not indicated until blood glucose concentration is less than 250 mg/dl, then begin 5% dextrose infusion

#### **Bicarbonate Therapy**

Indication: administer if plasma bicarbonate concentration is less than 12 mEq/L or total venous CO<sub>2</sub> concentration is less than 12 mmol/L; if not known, do not administer unless animal is severely ill and then only once

**Amount:** mEq HCO<sub>3</sub><sup>-</sup> = body weight  $\{kg\} \times 0.4 \times (12 - animal's HCO<sub>3</sub><sup>-</sup>) \times 0.5$ ; if animal's HCO<sub>3</sub><sup>-</sup> or total CO<sub>2</sub> concentration is unknown, use 10 in place of  $\{12 - animal's HCO<sub>3</sub><sup>-</sup>\}$ 

Administration: add to intravenous fluids and give over 6 hours; do not give as bolus infusion

**Retreatment:** only if plasma bicarbonate concentration remains less than 12 mEq/L after 6 hours of therapy

#### Insulin Therapy

Type: regular crystalline insulin

#### **Administration Technique**

Intermittent intramuscular technique: initial dose, 0.2 U/kg intramuscularly; then 0.1 U/kg intramuscularly hourly until blood glucose concentration is less than 250 mg/dl; then switch to regular insulin administered subcutaneously q6-8h.

Low-dose intravenous infusion technique: to prepare infusion, add 2.2 U/kg (dogs) or 1.1 U/kg (cats) of regular insulin to 250 ml of 0.9% saline; run 50 ml through the drip set and discard; then administer via infusion or syringe pump through a line separate from that used for fluid therapy at an initial rate of 10 ml/hour; adjust infusion rate according to hourly blood glucose measurements; switch to subcutaneous regular insulin q6-8h once blood glucose is less than 250 mg/dl or continue insulin infusion at a decreased rate to prevent hypoglycemia until the insulin preparation is exchanged for a longer-acting product.

Goal: gradual decline in blood glucose concentration, preferably around 75 mg/dl/hour until concentration is less than 250 mg/dl

#### **Ancillary Therapy**

Concurrent pancreatitis is common in diabetic ketoacidosis; nothing by mouth and aggressive fluid therapy usually indicated

Concurrent infections are common in diabetic ketoacidosis; use of broad-spectrum, parenteral antibiotics usually indicated Additional therapy may be needed, depending on nature of concurrent disorders

#### **Patient Monitoring**

Blood glucose measurement q1-2h initially; adjust insulin therapy and begin dextrose infusion when decreases below 250 mg/dl

Hydration status, respiration, pulse q2-4h; adjust fluids accordingly

Serum electrolyte and total venous  $CO_2$  concentrations q6-12h; adjust fluid and bicarbonate therapy accordingly

Urine output, glycosuria, ketonuria q2-4h; adjust fluid therapy accordingly

Body weight, packed cell volume, temperature, and blood pressure daily

Additional monitoring, depending on concurrent disease

Hypotonic fluids (e.g., 0.45% saline) are rarely indicated in dogs and cats with DKA, even when severe hyperosmolality is present. Hypotonic fluids do not provide adequate amounts of sodium to correct the sodium deficiency, restore normal fluid balance, or stabilize blood pressure. Rapid administration of hypotonic fluids can also cause a rapid decrease in the osmolality of extracellular fluid (ECF), which may result in cerebral edema, deterioration in mentation, and eventually coma. Hyperosmolality is best treated with isotonic fluids and the judicious administration of insulin. Fluid administration should be directed at gradually replacing hydration deficits over 24 hours while also supplying maintenance fluid needs and matching ongoing losses. Rapid replacement of fluids is rarely indicated unless the dog or cat is in shock. Once the animal is out of this critical phase, fluid replacement should be decreased in an effort to correct the fluid imbalance in a slow but steady manner. As a general rule of thumb, a fluid rate of 1.5 to 2 times maintenance (i.e., 60 to 100 ml/kg q24h) is typically chosen initially, with subsequent adjustments based on frequent assessment of hydration status, urine output, severity of azotemia, and persistence of vomiting and diarrhea.

## **Potassium Supplementation**

Most dogs and cats with DKA initially have either normal or decreased serum potassium concentrations. During therapy for DKA the serum potassium concentration decreases because of rehydration (dilution), insulin-mediated cellular uptake of potassium (with glucose), continued urinary losses, and correction of acidemia (translocation of potassium into the intracellular fluid compartment; Fig. 52-18). Severe hypokalemia is the most common complication that devel-

ops during the initial 24 to 36 hours of treatment of DKA. Dogs and cats with hypokalemia require aggressive potassium replacement therapy to replace deficits and to prevent worsening, life-threatening hypokalemia after initiation of insulin therapy. The exception to potassium supplementation of fluids is hyperkalemia associated with oliguric renal failure. Potassium supplementation should initially be withheld in these dogs and cats until glomerular filtration is



BOX 52-10

Common Clinicopathologic Abnormalities Identified in Dogs and Cats with Diabetic Ketoacidosis

Neutrophilic leukocytosis, signs of toxicity if septic Hemoconcentration Hyperglycemia Hypercholesterolemia, lipemia Increased alkaline phosphatase activity Increased alanine aminotransferase activity Increased blood urea nitrogen and serum creatinine concentrations Hyponatremia Hypochloremia Hypokalemia Metabolic acidosis (decreased total carbon dioxide concentration) Hyperlipasemia Hyperamylasemia **Hyperosmolality** Glycosuria Ketonuria Urinary tract infection

restored, urine production increases, and hyperkalemia is resolving.

Ideally, the amount of potassium required should be based on actual measurement of the serum potassium concentration. If an accurate measurement of serum potassium is not available, 40 mEq of potassium should initially be added to each liter of intravenous fluids. Normal saline solution does not contain potassium, and Ringer's solution contains 4 mEq of potassium per liter; thus these fluids should be supplemented with 40 mEq and 36 mEq of potassium, respectively. Subsequent adjustments in potassium supplementation should be based on measurement of serum potassium, preferably every 6 to 8 hours until the dog or cat is stable and serum electrolytes are in the normal range.

## **Phosphate Supplementation**

Most dogs and cats with DKA have either normal or decreased serum phosphorus concentrations on pretreatment testing. Within 24 hours of initiating treatment for DKA, serum phosphorus concentration can decline to severe levels (i.e., <1 mg/dl) as a result of the dilutional effects of fluid therapy, the intracellular shift of phosphorus following the initiation of insulin therapy, and continuing renal and gastrointestinal loss (see Fig. 52-18). Hypophosphatemia affects primarily the hematologic and neuromuscular systems in dogs and cats. Hemolytic anemia is the most common problem and can be life threatening if not recognized and treated. Weakness, ataxia, and seizures may also be observed. Severe hypophosphatemia may be clinically silent in many animals

Phosphate therapy is indicated if clinical signs or hemolysis are identified or if the serum phosphorus concentration decreases to less than 1.5 mg/dl. Phosphate is supplemented

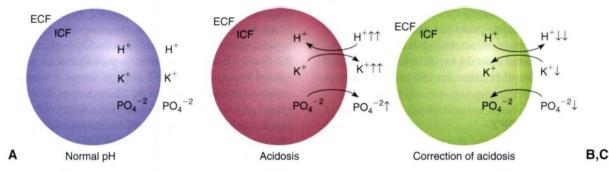


FIG 52-18

Redistribution of extracellular fluid (ECF) and intracellular fluid (ICF) hydrogen, potassium, and phosphate ions in response to a decrease in ECF pH (i.e., acidosis), an increase in ECF glucose and osmolality, and the translocation of water from the ICF to the ECF compartment and subsequent correction of acidosis and the intracellular shift of glucose and electrolytes with insulin treatment. **A,** Normal ECF pH. **B,** ECF H+ concentration increases during acidosis, causing H+ to move into cells and down its concentration gradient. Increase in ECF glucose and osmolality causes extracellular shift of water, K+, and  $PO_4^{+2}$ . **C,** ECF H+ concentration decreases during correction of acidosis, causing H+ to move out of cells. Insulin administration and correction of acidemia cause an intracellular shift of glucose, K+ and  $PO_4^{+2}$ , decreasing ECF K+ and  $PO_4^{+2}$  concentration. (Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004,WB Saunders.)

by IV infusion. Potassium and sodium phosphate solutions contain 3 mmol of phosphate and either 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The recommended dosage for phosphate supplementation is 0.01 to 0.03 mmol of phosphate per kilogram of body weight per hour, preferably administered in calcium-free IV fluids (e.g., 0.9% sodium chloride). In dogs and cats with severe hypophosphatemia it may be necessary to increase the dosage to 0.03 to 0.12 mmol/kg/hour. Because the dose of phosphate necessary to replete an animal and the animal's response to therapy cannot be predicted, it is important to initially monitor the serum phosphorus concentration every 8 to 12 hours and adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, and metastatic calcification. Serum total or (preferably) ionized calcium concentration should be measured at the same time as serum phosphorus concentration and the rate of phosphate infusion decreased if hypocalcemia is identified. Phosphorus supplementation is not indicated in dogs and cats with hypercalcemia, hyperphosphatemia, oliguria, or suspected tissue necrosis. If renal function is in question, phosphorus supplementation should not be done until the status of renal function and serum phosphorus concentration are known.

## **Magnesium Supplementation**

Plasma total and ionized magnesium concentrations may be within or below the reference range at the time DKA is diagnosed in the dog or cat, often decrease during the initial treatment of DKA, and typically normalize without treatment as the DKA resolves. Clinical signs of hypomagnesemia do not usually occur until the serum total and ionized magnesium concentration is less than 1.0 and 0.5 mg/dl, respectively, and even at these low levels many dogs and cats remain asymptomatic. I do not routinely treat hypomagnesemia in dogs or cats with DKA unless problems with persistent lethargy, anorexia, weakness, or refractory hypokalemia or hypocalcemia are encountered after 24 to 48 hours of fluid and insulin therapy and another cause for the problem cannot be identified (see p. 780).

## **Bicarbonate Therapy**

The clinical presentation of the dog or cat, in conjunction with the plasma bicarbonate or total venous  $CO_2$  concentration, should be used to determine the need for bicarbonate therapy. Bicarbonate supplementation is not recommended when plasma bicarbonate (or total venous  $CO_2$ ) is 12 mEq/L or greater, especially if the animal is alert. An alert dog or cat probably has a normal or near-normal pH in the cerebrospinal fluid (CSF). The acidosis in these animals is corrected through insulin and fluid therapy. Improvement in renal perfusion enhances urinary loss of ketoacids, and insulin therapy markedly diminishes the production of ketoacids. Acetoacetate and  $\beta$ -hydroxybutyrate are also metabolically usable anions, and 1 mEq of bicarbonate is generated from each 1 mEq of ketoacid metabolized.

When the plasma bicarbonate concentration is 11 mEq/L or less (total venous CO<sub>2</sub> is below 12), bicarbonate therapy should be initiated. Many of these animals have severe depression that may be a result of concurrent severe central nervous system acidosis. Metabolic acidosis should be corrected slowly, thereby avoiding major alterations in the pH of the CSF. Only a portion of the bicarbonate deficit is given initially over a 6-hour period. The bicarbonate deficit (i.e., the milliequivalents of bicarbonate initially needed to correct acidosis to the critical level of 12 mEq/L over a period of 6 hours) is calculated by the following formula:

### mEq bicarbonate = body weight (kg) $\times 0.4 \times (12 - \text{animal's})$ bicarbonate) $\times 0.5$

If the serum bicarbonate concentration is not known, the following formula should be used:

#### mEq bicarbonate = body weight (kg) $\times$ 2

The difference between the animal's serum bicarbonate concentration and the critical value of 12 mEq/L represents the treatable base deficit in DKA. If the animal's serum bicarbonate concentration is not known, the number 10 should be used for the treatable base deficit. The factor 0.4 corrects for the ECF space in which bicarbonate is distributed (40% of body weight). The factor 0.5 provides one half of the required dose of bicarbonate in the IV infusion. This technique allows a conservative dose to be given over a 6-hour period. Bicarbonate should never be given by bolus infusion. After 6 hours of therapy the acid-base status should be reevaluated and a new dose calculated. Once the plasma bicarbonate level is greater than 12 mEq/L, further bicarbonate supplementation is not indicated.

## INSULIN THERAPY

Insulin therapy is critical for the resolution of ketoacidosis. However, overzealous insulin treatment can cause severe hypokalemia, hypophosphatemia, and hypoglycemia during the first 24 hours of treatment—problems that can be minimized by appropriate fluid therapy, frequent monitoring of serum electrolytes and blood glucose concentrations, and modification of the initial insulin treatment protocol as indicated. Initiating appropriate fluid therapy should always be the first step in the treatment of DKA. Delaying insulin therapy for a minimum of 1 to 2 hours is recommended to allow the benefits of fluid therapy to begin to be realized before the glucose, potassium, and phosphorus-lowering effects of insulin therapy commence. Additional delays and decisions on the initial dosage of insulin administered are based on serum electrolyte results. If the serum potassium concentration is within the normal range after 2 hours of fluid therapy, insulin treatment should commence as described in the subsequent paragraphs. If hypokalemia persists, insulin therapy can be delayed an additional 1 to 2 hours to allow fluid therapy to replenish potassium, the initial insulin dose can be reduced to dampen the intracellular shift of potassium and phosphorus, or both can be

done. However, insulin therapy should be started within 4 hours of initiating fluid therapy.

The amount of insulin needed by an individual animal is difficult to predict. Therefore an insulin preparation with a rapid onset of action and a brief duration of effect is ideal for making rapid adjustments in the dose and frequency of administration to meet the needs of that particular dog or cat. Rapid-acting regular crystalline insulin meets these criteria and is recommended for the treatment of DKA.

Insulin protocols for the treatment of DKA include the hourly intramuscular technique, the continuous low-dose IV infusion technique, and the intermittent intramuscular then subcutaneous technique. All three routes (IV, intramuscular, subcutaneous) of insulin administration are effective in decreasing blood glucose and ketone concentrations. Successful management of DKA is *not* dependent on the route of insulin administration. Rather, it is dependent on proper treatment of each disorder associated with DKA.

## Intermittent Intramuscular Regimen

Dogs and cats with severe DKA should receive an initial regular crystalline insulin loading dose of 0.2 U/kg followed by 0.1 U/kg every hour thereafter. The insulin dose can be reduced by 25% to 50% for the first 2 to 3 injections if hypokalemia is a concern. The insulin should be administered into the muscles of the rear legs to ensure that the injections are penetrating muscle rather than fat or subcutaneous tissue. Diluting regular insulin 1:10 with sterile saline and using 0.3 ml U100 insulin syringes are helpful when small doses of insulin are required. The blood glucose concentration should be measured every hour using a point-of-care chemistry analyzer or portable blood glucose monitoring device and the insulin dosage adjusted accordingly. The goal of initial insulin therapy is to slowly lower the blood glucose concentration to the range of 200 to 250 mg/dl, preferably over a 6- to 10-hour period. An hourly decline of 50 mg/dl in the blood glucose concentration is ideal. This provides a steady moderate decline, with no major shifts in osmolality. A declining blood glucose concentration also ensures that lipolysis and the supply of FFAs for ketone production have been effectively turned off. Glucose concentrations, however, decrease much more rapidly than do ketone levels. In general, hyperglycemia is corrected within 12 hours, but ketosis may take 48 to 72 hours to resolve.

Once the initial hourly insulin therapy brings the blood glucose concentration near 250 mg/dl, hourly administration of regular insulin should be discontinued and regular insulin given every 4 to 6 hours intramuscularly or, if hydration status is good, every 6 to 8 hours subcutaneously. The initial dose is usually 0.1 to 0.3 U/kg, with subsequent adjustments based on blood glucose concentrations. In addition, at this point the IV infusion solution should have enough 50% dextrose added to create a 5% dextrose solution (100 ml of 50% dextrose added to each liter of fluids). The blood glucose concentration should be maintained between 150 and 300 mg/dl until the animal is stable and eating. Usually, a 5% dextrose solution is adequate in maintaining the desired

blood glucose concentration. If the blood glucose concentration dips below 150 mg/dl or rises above 300 mg/dl, the insulin dose can be lowered or raised accordingly. Dextrose helps minimize problems with hypoglycemia and allows insulin to be administered on schedule. Delaying the administration of insulin delays correction of the ketoacidotic state.

## Constant Low-Dose Insulin Infusion Technique

Constant IV infusion of regular crystalline insulin is also effective in decreasing blood glucose concentrations. To prepare the infusion, regular crystalline insulin (2.2 U/kg for dogs; 1.1 U/kg for cats) is added to 250 ml of 0.9% saline and initially administered at a rate of 10 ml/hour in a line separate from that used for fluid therapy. This provides an insulin infusion of 0.05 (cat) and 0.1 (dog) U/kg/hour, an infusion rate that has been shown to produce plasma insulin concentrations between 100 and 200  $\mu$ U/ml in dogs. Because insulin adheres to glass and plastic surfaces, approximately 50 ml of the insulin-containing fluid should be run through the drip set before it is administered to the animal. The rate of insulin infusion can be reduced for the initial 2 to 3 hours if hypokalemia is a concern. Two separate catheters are recommended for treatment: a peripheral catheter for insulin administration and a central catheter for fluid administration and blood sampling. An infusion or syringe pump should be used to ensure a constant rate of insulin infusion.

Adjustments in the infusion rate are based on hourly measurements of blood glucose concentration; an hourly decline of 50 mg/dl in the blood glucose concentration is ideal. Once the blood glucose concentration approaches 250 mg/dl, the insulin infusion can be discontinued and regular insulin given every 4 to 6 hours intramuscularly or every 6 to 8 hours subcutaneously, as discussed for the hourly intramuscular protocol. Alternatively, the insulin infusion can be continued (at a decreased rate to prevent hypoglycemia) until the insulin preparation is exchanged for a longeracting product. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dl, as discussed in the section on hourly intramuscular insulin technique.

## Intermittent Intramuscular/ Subcutaneous Technique

The intermittent intramuscular followed by intermittent subcutaneous insulin technique is less labor intensive than the other techniques for insulin administration, but the decrease in blood glucose can be rapid and the risk of hypoglycemia is greater. The initial regular crystalline insulin dose is 0.25 U/kg, administered intramuscularly. Subsequent intramuscular injections are repeated every 4 hours. Usually, insulin is administered intramuscularly only once or twice. Once the animal is rehydrated, the insulin is administered subcutaneously rather than intramuscularly every 6 to 8 hours. Subcutaneous administration is not recommended

initially because of problems with insulin absorption from subcutaneous sites of deposition in a dehydrated dog or cat. The dosage of intramuscular or subcutaneous insulin is adjusted according to blood glucose concentrations, which initially should be measured hourly beginning with the first intramuscular injection. An hourly decline of 50 mg/dl in the blood glucose concentration is ideal. Subsequent insulin dosages should be decreased by 25% to 50% if this goal is exceeded. Dextrose should be added to the IV fluids once the blood glucose concentration approaches 250 mg/dl, as discussed in the section on hourly intramuscular insulin technique.

## **Initiating Longer-Acting Insulin**

Longer-acting insulin (e.g., NPH, lente, PZI) should not be administered until the dog or cat is stable; eating; maintaining fluid balance without any IV infusions; and no longer acidotic, azotemic, or electrolyte-deficient. The initial dose of the longer-acting insulin is similar to the regular insulin dose being used just before switching to the longer-acting insulin. Subsequent adjustments in the longer-acting insulin dose should be based on clinical response and measurement of blood glucose concentrations, as described on p. 775.

#### **CONCURRENT ILLNESS**

Therapy for DKA frequently involves the management of concurrent, often serious illness. Common concurrent illnesses in dogs and cats with DKA include bacterial infection; pancreatitis; congestive heart failure; renal failure; cholangiohepatitis; and insulin-antagonistic disorders, most notably hyperadrenocorticism, hyperthyroidism, and diestrus. It may be necessary in such animals to modify the therapy for DKA (e.g., fluid therapy in animals with concurrent heart failure) or implement additional therapy (e.g., antibiotics), depending on the nature of the concurrent illness. Insulin therapy, however, should never be delayed or discontinued. Resolution of ketoacidosis can be achieved only through insulin therapy. If nothing is to be given per os, insulin therapy should be continued and the blood glucose concentration maintained with IV dextrose infusions. If a concurrent insulin-antagonistic disease is present, it may be necessary to eliminate the disease while the animal is still ill to improve insulin effectiveness and resolve the ketoacidosis.

## COMPLICATIONS OF THERAPY FOR DIABETIC KETOACIDOSIS

Complications caused by therapy for DKA are common and include hypoglycemia, central nervous system signs secondary to cerebral edema, severe hypokalemia, severe hypernatremia and hyperchloremia, and hemolytic anemia resulting from hypophosphatemia. Complications usually result from overly aggressive treatment, inadequate monitoring of the animal's condition, and failure to reevaluate biochemical parameters in a timely manner. DKA is a complex disorder that is associated with a high mortality rate if improperly managed. To minimize the risk of therapeutic complications

and improve the chances of a successful response to therapy, all abnormal parameters should be slowly returned toward normal over a period of 24 to 48 hours, the physical and mental status of the animal must be evaluated frequently (at least three to four times daily), and biochemical parameters (e.g., blood glucose, serum electrolyte, blood gas values) must be evaluated in a timely fashion. During the initial 24 hours the blood glucose concentration should be measured every 1 to 2 hours and serum electrolyte and blood gas values measured every 6 to 8 hours, with modifications in fluid, insulin, and bicarbonate therapy made accordingly.

## **Prognosis**

DKA remains one of the most difficult metabolic therapeutic challenges in veterinary medicine. Despite all precautions and diligent therapy, a fatal outcome is sometimes inevitable. Approximately 30% of cats and dogs with severe DKA die or are euthanized during the initial hospitalization. Death is usually the result of a severe underlying illness (e.g., oliguric renal failure, necrotizing pancreatitis), severe metabolic acidosis (i.e., arterial blood pH less than 7), or complications that develop during therapy (e.g., cerebral edema, hypokalemia). Nevertheless, if logical therapy is implemented and animals are monitored carefully, a positive outcome is attainable.

## INSULIN-SECRETING BETA-CELL NEOPLASIA

## **Etiology**

Functional tumors arising from the  $\beta$  cells of the pancreatic islets are malignant tumors that secrete insulin independent of the typically suppressive effects of hypoglycemia.  $\beta$  cell tumors, however, are not completely autonomous and respond to provocative stimuli such as an increase in blood glucose by secreting insulin, often in excessive amounts. Immunohistochemical analysis of  $\beta$  cell tumors has revealed a high incidence of multihormonal production, including pancreatic polypeptide, somatostatin, glucagon, serotonin, and gastrin. However, insulin has been identified as the most common product demonstrated within the neoplastic cells, and clinical signs are primarily those that result from insulininduced hypoglycemia.

Insulin-secreting  $\beta$  cell tumors are uncommon in dogs and rare in cats. Virtually all  $\beta$  cell tumors in dogs are malignant, and most dogs have microscopic or grossly visible metastatic lesions at the time of surgery. The most common metastatic sites are the regional lymphatics and lymph nodes, liver, and peripancreatic mesentery. Pulmonary metastasis is uncommon and occurs late in the disease. In most dogs hypoglycemia recurs weeks to months after surgical excision of the tumor. The high prevalence of metastatic lesions at the time afflicted dogs are initially examined results, in part, from the typically protracted time it takes for clinical signs to develop and the interval between the time a client initially observes signs and seeks assistance from a veterinarian. Most



BOX 52-11

Clinical Signs Associated with Insulin-Secreting Tumors in Dogs

Seizures\* Weakness\*

Collapse Ataxia

Polyphagia

Weight gain

Muscle fasciculations

Posterior weakness (neuropathy)

Lethargy

Nervousness

Bizarre behavior

dogs are symptomatic for 1 to 6 months before being brought to a veterinarian.

#### **Clinical Features**

## SIGNALMENT OF TREATMENT

 $\beta$  cell tumors typically occur in middle-aged or older dogs. The median age at the time of diagnosis of a  $\beta$  cell tumor in 97 dogs in our series was 10 years with an age range of 3 to 14 years. No sex-related predilection is seen.  $\beta$  cell tumors are most commonly diagnosed in large breeds of dogs such as the German Shepherd Dog, Labrador Retriever, and Golden Retriever.  $\beta$  cell tumors have been reported in Siamese and mixed-breed cats older than 10 years of age.

## **CLINICAL SIGNS**

Clinical signs are caused by hypoglycemia and an increase in circulating catecholamine concentrations and include seizures, weakness, collapse, ataxia, muscle fasciculations, and bizarre behavior (Box 52-11). The severity of clinical signs depends on the duration and severity of hypoglycemia. Dogs with chronic hypoglycemia or with recurring episodes appear to tolerate low blood glucose concentrations (20 to 30 mg/ dl) for prolonged periods without clinical signs, and only small additional changes in the blood glucose concentration are then required to produce symptomatic episodes. Fasting, excitement, exercise, and eating may trigger the development of clinical signs. Because of the compensatory counterregulatory mechanisms that are designed to increase the blood glucose concentration when hypoglycemia develops, clinical signs tend to be episodic and are generally observed for only a few seconds to minutes. If these counterregulatory mechanisms are inadequate, seizures occur as the blood glucose concentration continues to decrease. Seizures are often selflimiting, lasting from 30 seconds to 5 minutes, and may stimulate further catecholamine secretion and the activation of other counterregulatory mechanisms that increase the blood glucose concentration above critical levels.

#### PHYSICAL EXAMINATION

Physical examination findings in animals with  $\beta$  cell tumors are surprisingly unremarkable; dogs are usually free of visible or palpable abnormalities. Weakness and lethargy are the most common findings and are identified in approximately 40% and 20% of our cases, respectively. Collapsing episodes and seizures may occur during the examination but are uncommon. Weight gain is evident in some dogs and is probably a result of the potent anabolic effects of insulin.

## **Peripheral Neuropathy**

Peripheral neuropathies have been observed in dogs with β cell tumors and may cause paraparesis to tetraparesis; facial paresis to paralysis; hyporeflexia to areflexia; hypotonia; and muscle atrophy of the appendicular, masticatory, and/or facial muscles. Sensory nerves may also be affected. Onset of clinical signs may be acute (i.e., days) or insidious (i.e., weeks to months). The pathogenesis of the polyneuropathy is not known. Proposed theories include metabolic derangements of the nerves induced by chronic and severe hypoglycemia or some other tumor-induced metabolic deficiency, an immune-mediated paraneoplastic syndrome resulting from shared antigens between tumor and nerves, or toxic factors produced by the tumor that deleteriously affect the nerves. Treatment is aimed at surgical removal of the  $\beta$  cell tumor. Prednisone therapy (initially 1 mg/kg q24h) may also improve clinical signs.

#### **CLINICAL PATHOLOGY**

Results of the CBC and urinalysis are usually normal. The only consistent abnormality identified in serum biochemistry profiles is hypoglycemia. The median initial blood glucose concentration in 97 of our dogs with a  $\beta$  cell tumor was 38 mg/dl, with a range of 15 to 78 mg/dl. Ninety percent of the dogs had a random blood glucose concentration less than 60 mg/dl. Dogs with  $\beta$  cell tumors occasionally have a blood glucose concentration of 60 to 80 mg/dl. Such a finding does not rule out hypoglycemia as a cause of episodic weakness or seizure activity. Fasting with hourly evaluations of the blood glucose concentration should be carried out in dogs with suspected hypoglycemia. The time required to induce hypoglycemia with fasting in dogs with a  $\beta$  cell tumor depends in part on the extent of disease at the time the dog is examined and ranges from a few hours to longer than 24 hours. The remainder of the serum biochemistry profile is usually normal. Hypoalbuminemia, hypophosphatemia, hypokalemia, and increased alkaline phosphatase and alanine aminotransferase activities may occur, but these findings are considered nonspecific and not helpful in arriving at a definite diagnosis. A correlation between increased liver enzyme activities and metastasis of  $\beta$  cell tumors to the liver has not been established.

#### Diagnosis

The diagnosis of a  $\beta$  cell tumor requires initial confirmation of hypoglycemia, followed by documentation of inappropriate insulin secretion and identification of a pancreatic mass

<sup>\*</sup>Common clinical signs.

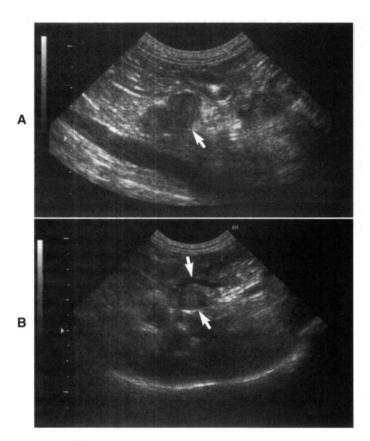


FIG 52-19
Ultrasonogram of the pancreas showing an islet β-cell tumor (arrow) (A) and an enlarged hepatic lymph node (arrows)
(B) resulting from metastasis of the β-cell tumor to the liver in a 9-year-old Cocker Spaniel.

using ultrasonography or laparotomy. Considering the potential differential diagnoses for hypoglycemia (see Box 52-2), a tentative diagnosis of a B cell tumor can often be made on the basis of the history, physical examination findings, and an absence of abnormalities other than hypoglycemia shown by routine blood tests. Abdominal ultrasonography can be used to identify a mass in the region of the pancreas and to look for evidence of potential metastatic disease in the liver and surrounding structures (Fig. 52-19). Because of the small size of most B cell tumors, abdominal ultrasonographic findings are often interpreted as normal, although a pancreatic mass or metastatic lesion can be found at surgery. A normal abdominal ultrasonographic finding does not rule out the diagnosis of a B cell tumor. Although computed tomographic imaging was better than ultrasonography or somatostatin receptor scintigraphy at identifying primary tumors, false-positive identification of metastatic sites was unacceptably high in one study (Robben et al., 2005). Thoracic radiographs are of minimal value in documenting metastatic disease, primarily because identifiable metastatic nodules in the lung occur late in the disease.

The diagnosis of a cell tumor is established by evaluating the serum insulin concentration at a time when hypoglycemia is present. Hypoglycemia suppresses insulin

secretion in normal animals, with the degree of suppression directly related to its severity. Hypoglycemia fails to have this same suppressive effect on insulin secretion if the insulin is synthesized and secreted from autonomous neoplastic cells because tumor cells that produce and secrete insulin are less responsive to hypoglycemia than are normal B cells. Invariably, the dog with a B cell tumor will have an inappropriate excess of insulin relative to that needed for a particular blood glucose concentration. Confidence in identifying an inappropriate excess of insulin depends on the severity of the hypoglycemia; the lower the blood glucose concentration, the more confident the clinician can be in identifying inappropriate hyperinsulinemia, especially when the serum insulin concentration falls in the normal range. If the blood glucose concentration is low and the insulin concentration is in the upper half of the normal range or increased, the animal has a relative or absolute excess of insulin that can best be explained by the presence of an insulin-secreting B cell tumor.

Most dogs with B cell neoplasia are persistently hypoglycemic. If the blood glucose concentration is less than 60 mg/ dl (preferably less than 50 mg/dl), serum should be submitted to a commercial veterinary endocrine laboratory for determination of glucose and insulin concentrations. If the blood glucose concentration is greater than 60 mg/dl, fasting may be necessary to induce hypoglycemia. Blood glucose concentrations should be evaluated hourly during the fast and blood obtained for glucose and insulin determination when the blood glucose concentration decreases to less than 50 mg/dl. It is important to remember that blood glucose results obtained from portable home blood glucosemonitoring devices are often lower than results obtained using benchtop methodologies. A blood sample for submission to a commercial laboratory for glucose and insulin determinations should not be obtained until the blood glucose measured on these devices is less than 40 mg/dl. Once hypoglycemia has been induced, the dog can be fed several small meals over the next 1 to 3 hours to prevent a marked increase in the blood glucose concentration and a potential postprandial reactive hypoglycemia.

Serum insulin concentrations must be evaluated simultaneously in relation to the blood glucose concentration. The serum insulin and glucose concentrations in the healthy fasted dog are usually between 5 and 20 U/ml and 70 and 110 mg/dl, respectively. Fnding a serum insulin concentration greater than 20 µU/ml in a dog with a corresponding blood glucose concentration less than 60 mg/dl (preferably less than 50 mg/dl) in combination with appropriate clinical signs and clinicopathologic findings strongly supports the diagnosis of a B cell tumor. A B cell tumor is also possible if the serum insulin concentration is in the high-normal range (10 to 20 µU/ml). Insulin values in the low-normal range (5 to 10 µU/ml) may be found in animals with other causes of hypoglycemia as well as a B cell tumor. Carefully reviewing the history, physical examination findings, and diagnostic tests results and, if necessary, repeating serum glucose and insulin measurements when hypoglycemia is

more severe will usually identify the cause of the hypoglycemia. Any serum insulin concentration that is below the normal range (typically less than 5  $\mu U/ml)$  is consistent with insulinopenia and does not indicate the presence of a  $\beta$  cell tumor. Similar guidelines are used for cats with a suspected  $\beta$  cell tumor.

#### **Treatment**

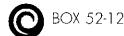
#### **OVERVIEW OF TREATMENT**

Treatment options for a B cell tumor include surgical exploration, medical treatment for chronic hypoglycemia, or both. Surgery offers a chance to cure dogs with a resectable solitary mass. In dogs with nonresectable tumors or with obvious metastatic lesions, removal of as much abnormal tissue as possible frequently results in remission, or at least alleviation, of clinical signs and an improved response to medical therapy. Survival time is longer in dogs undergoing surgical exploration and tumor debulking followed by medical therapy, compared with dogs that receive only medical treatment. Despite these benefits, surgery remains a relatively aggressive mode of treatment, in part because of the high prevalence of metastatic disease, the older age of many dogs at the time β cell neoplasia is diagnosed, and the potential for postoperative pancreatitis. As a general rule, I am less inclined to recommend surgery in aged dogs (i.e., 12 years and older), dogs with metastatic disease identified by ultrasonography, and dogs with significant concurrent disease. (See Suggested Readings for detailed information on surgical techniques.)

# PERIOPERATIVE MANAGEMENT OF DOGS UNDERGOING SURGERY

Until surgery is performed, the dog or cat with a  $\beta$  cell tumor must be protected from episodes of severe hypoglycemia. This can usually be accomplished through the frequent feeding of small meals and administration of glucocorticoids (Box 52-12). The IV administration of a balanced electrolyte solution containing 2.5% to 5% dextrose is important during the perioperative period. The goal of the dextrose infusion is to prevent clinical signs of hypoglycemia and maintain the blood glucose concentration at greater than 35 mg/dl, not to reestablish a normal blood glucose concentration.

If the dextrose infusion is ineffective in preventing severe hypoglycemia, a constant rate infusion of glucagon should be considered. Glucagon is a potent stimulant of hepatic gluconeogenesis and is effective in maintaining normal blood glucose concentrations in dogs with  $\beta$  cell neoplasia when administered by constant-rate infusion. Lyophilized glucagon USP (1 mg) is reconstituted with the diluent provided by the manufacturer (Eli Lilly), and the solution is added to 1 L of 0.9% saline, making a 1 µg/ml solution that can be administered by syringe pump. The initial dose is 5 to 10 ng/kg of body weight/minute. The dose is adjusted, as needed, to maintain the blood glucose concentration within the normal range. When discontinuing glucagon, the dose should be gradually decreased over 1 to 2 days.



Long-term Medical Therapy for Dogs with β-Cell Neoplasia

#### **Standard Treatments**

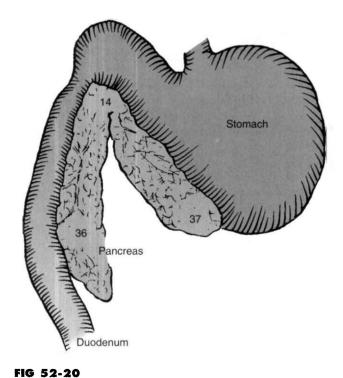
- 1. Dietary therapy
  - Feed canned or dry food in three to six small meals daily
  - Avoid foods containing monosaccharides, disaccharides, propylene glycol and corn syrup
- 2. Limit exercise
- 3. Glucocorticoid therapy
  - a. Prednisone, 0.5 mg/kg divided into two doses initially
  - Gradually increase dose and frequency of administration, as needed
  - c. Goal is to control clinical signs, not to reestablish euglycemia
  - d. Consider alternative treatments if signs of iatrogenic hypercortisolism become severe or glucocorticoids become ineffective

#### **Additional Treatments**

- 1. Diazoxide therapy
  - a. Continue standard treatment; reduce glucocorticoid dose to minimize adverse signs
  - b. Diazoxide, 5 mg/kg q12h initially
  - Gradually increase dose as needed, not to exceed 60 mg/kg/day
  - d. Goal is to control clinical signs, not to reestablish euglycemia
- 2. Somatostatin therapy
  - a. Continue standard treatment; reduce glucocorticoid dose to minimize adverse signs
  - b. Octreotide (Novartis Pharmaceuticals), 10 to 40 μg/ dog administered subcutaneously q12h to q8h
- 3. Streptozotocin therapy
  - a. Continue standard treatment; reduce glucocorticoid dose to minimize adverse signs
  - b. 0.9% saline diuresis for 3 hours, then streptozotocin, 500 mg/m², in 0.9% saline and administered intravenously over 2 hours, then 0.9% saline diuresis for 2 additional hours
  - c. Administer antiemetics immediately after streptozotocin administration to minimize vomiting
  - Repeat treatment every 3 weeks until hypoglycemia resolves or adverse reactions develop (e.g., pancreatitis, renal failure)

#### **POSTOPERATIVE COMPLICATIONS**

The most common postoperative complications are pancreatitis, hyperglycemia, and hypoglycemia. The development of these complications is directly related to the expertise of the surgeon, the location of the tumor in the pancreas (i.e., peripheral lobe versus central region; Fig. 52-20), the presence or absence of functional metastatic lesions, and the adequacy of fluid therapy during the perioperative period.



Tumor location in 87 dogs with islet B-cell tumors. (Adapted from Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB

Saunders.)

Severe pancreatitis occurs most commonly with attempts to remove tumors located in the central region of the pancreas, where the blood supply and pancreatic ducts are located. Tumors located in the central region of the pancreas should be considered inoperable because of the high prevalence of postoperative life-threatening pancreatitis despite appropriate treatment aimed at preventing its development, including aggressive fluid therapy, nothing by mouth for up to 72 hours after surgery, and appropriate dietary therapy during the ensuing week. The reader is referred to Chapter 40 for information on the treatment of pancreatitis.

The development of transient diabetes mellitus after surgical removal of a B cell tumor is not an indication of cure. It is believed to result from inadequate insulin secretion by atrophied normal B cells. Removal of all, or most, of the neoplastic cells acutely deprives the animal of insulin. Until the atrophied normal cells regain their secretory abilities, the animal will be hypoinsulinemic and may require exogenous insulin injections to maintain euglycemia. Insulin therapy is initiated postoperatively only if hyperglycemia and glycosuria persist for longer than 2 or 3 days beyond the time that all dextrose-containing IV fluids have been discontinued. Initial insulin therapy should be conservative—that is, 0.25 U of NPH or lente insulin per kilogram of body weight given once daily. Subsequent adjustments in insulin therapy should be made according to clinical response and blood glucose determinations (see p. 774). The need for insulin treatment is usually transient, lasting from a few days to several months.

Rarely, a dog will remain diabetic for more than a year. Client evaluation of the pet's urine glucose level is helpful in identifying when insulin therapy is no longer needed. Failure to identify glucose in the urine in conjunction with the disappearance of polyuria and polydipsia is an indication to discontinue insulin therapy. If hyperglycemia and glycosuria recur, insulin therapy can be reinstituted but at a lower dose.

Dogs that remain hypoglycemic after surgical removal of a  $\beta$  cell tumor have functional metastatic lesions. The dextrose and/or glucagon infusion should be continued postoperatively until pancreatitis has resolved (if present); the dog is stable, eating, and drinking; and medical treatment for chronic hypoglycemia can be initiated (see Box 52-12).

# MEDICAL TREATMENT FOR CHRONIC HYPOGLYCEMIA

Medical treatment for chronic hypoglycemia should be initiated if surgery is not performed or when clinical signs of hypoglycemia recur following surgery. The goals of medical treatment are to reduce the frequency and severity of clinical signs of hypoglycemia and prevent an acute hypoglycemic crisis, not to establish euglycemia, per se. Medical treatment is palliative and minimizes hypoglycemia by increasing the absorption of glucose from the intestinal tract (frequent feedings); increasing hepatic gluconeogenesis and glycogenolysis (glucocorticoids); or inhibiting the synthesis, secretion, or peripheral cellular actions of insulin (glucocorticoids, diazoxide, somatostatin; see Box 52-12).

#### **Frequent Feedings**

Frequent feedings provide a constant source of calories as a substrate for the excess insulin secreted by  $\beta$  cell tumors. Diets that are high in fat, complex carbohydrates, and fiber will delay gastric emptying and slow intestinal glucose absorption, helping to minimize the postprandial increase in the portal blood glucose concentration and the stimulation of insulin secretion by the tumor. Simple sugars are rapidly absorbed, have a potent stimulatory effect on insulin secretion by neoplastic  $\beta$  cells, and should be avoided. A combination of canned and dry dog food, fed in three to six small meals daily, is recommended. Daily caloric intake should be controlled because hyperinsulinemia promotes obesity. Exercise should be limited to short walks on a leash.

# **Glucocorticoid Therapy**

Glucocorticoid therapy should be initiated when dietary manipulations are no longer effective in preventing clinical signs of hypoglycemia. Glucocorticoids antagonize the effects of insulin at the cellular level, stimulate hepatic glycogenolysis, and indirectly provide the necessary substrates for hepatic gluconeogenesis. Prednisone is most often used at an initial dose of 0.25 mg/kg q12h. Adjustments in the dose are based on clinical response. The dose of prednisone required to control clinical signs increases with time in response to growth of the tumor and its metastatic sites. Eventually, the adverse effects of prednisone, specifically polyuria and poly-

dipsia, become unacceptable to clients. When this occurs, the dose of prednisone should be reduced but not stopped and additional therapy considered.

# Diazoxide Therapy

Diazoxide (Proglycem; Baker Norton Pharmaceuticals) is a benzothiadiazide diuretic that inhibits insulin secretion, stimulates hepatic gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose. The net effect is hyperglycemia. Unfortunately, diazoxide is difficult to procure and is expensive. The initial dose is 5 mg/kg q12h. The dose is adjusted according to clinical response but should not exceed 60 mg/kg/day. The most common adverse reactions to diazoxide are anorexia and vomiting. Administering the drug with a meal or decreasing the dose, at least temporarily, is usually effective in controlling adverse gastrointestinal signs.

# Somatostatin Therapy

Octreotide (Sandostatin; Novartis Pharmaceuticals) is an analog of somatostatin that inhibits the synthesis and secretion of insulin by normal and neoplastic  $\beta$  cells. The responsiveness of  $\beta$  cell tumors to the suppressive effects of octreotide depends on the presence of membrane receptors for somatostatin on the tumor cells. Octreotide at a dose of 10 to 40  $\mu g/dog$ , administered subcutaneously two to three times a day, has alleviated hypoglycemia in approximately 40% to 50% of treated dogs. Adverse reactions have not been seen at these doses. Octreotide is not a viable option for most clients because of cost.

#### Streptozotocin Therapy

Streptozotocin is a naturally occurring nitrosourea that selectively destroys pancreatic  $\beta$  cells. The treatment protocol for  $\beta$  cell tumors in dogs involves a 0.9% saline diuresis for 7 hours with streptozotocin (500 mg/m<sup>2</sup>) administered over a 2-hour period beginning 3 hours after initiating the diuresis. Antiemetics are administered immediately after streptozotocin administration to minimize vomiting. Streptozotocin treatment is repeated every 3 weeks. The effectiveness of streptozotocin in improving hypoglycemia, controlling clinical signs, and prolonging survival time has been variable. Adverse reactions of streptozotocin treatment include vomiting, pancreatitis, diabetes mellitus, and renal failure. Renal failure is less likely when the drug is administered during fluid diuresis as described previously. (See Moore et al. [2002] in Suggested Readings for more information on the use of streptozotocin in treating β cell neoplasia in dogs.)

#### **Prognosis**

The long-term prognosis for  $\beta$  cell neoplasia is guarded to poor. Survival time is dependent, in part, on the willingness of the client to treat the disease. Tobin et al. (1999) reported a median survival time after diagnosis of only 74 days (range 8 to 508 days) in dogs treated medically, compared with 381 days (range 20 to 1758 days) in dogs that initially underwent surgery at a tertiary care center. The short survival time for

dogs treated medically was because many clients opted for euthanasia when seizures recurred or signs of iatrogenic hyperadrenocorticism developed. The extent to which surgery can alter the prognosis depends on the clinical stage of the disease, most notably the extent of metastatic lesions. Approximately 10% to 15% of dogs undergoing surgery for a  $\beta$  cell tumor die or are euthanized at the time of or within 1 month of surgery because of metastatic disease causing postoperative hypoglycemia that is refractory to medical management or because of complications related to pancreatitis. An additional 20% to 25% of dogs die or are euthanized within 6 months of surgery because of recurrence of clinical hypoglycemia that is refractory to medical management. The remaining 60% to 70% live beyond 6 months postoperatively, many beyond I year after surgery, before uncontrollable hypoglycemia develops, resulting in death or necessitating euthanasia. Additional surgery to debulk metastatic lesions may improve the animal's responsiveness to medical therapy and prolong the survival time in some dogs that become nonresponsive to medical treatment after the initial surgery.

# **GASTRIN-SECRETING NEOPLASIA**

Gastrin-secreting tumors (gastrinomas) are functional malignant tumors usually located in the pancreas of dogs and cats. Sites of metastasis include the liver, regional lymph nodes, spleen, and mesentery. Clinical signs result from the consequences of excess gastric hydrochloric acid secretion in response to excess secretion of gastrin by the tumor.

#### **Clinical Features**

The most consistent clinical signs are chronic vomiting, weight loss, anorexia, and diarrhea in an older animal (Box 52-13). Gastric and duodenal ulcers and esophagitis are common and may cause hematemesis, hematochezia, melena, and regurgitation. Acidification of intestinal contents may inactivate pancreatic digestive enzymes, precipitate bile salts,



BOX 52-13

Clinical Signs of Gastrinoma in Dogs and Cats

Vomiting\*
Anorexia\*

Lethargy, depression\*

Diarrhea\*

Weight loss\*

Melena

Hematemesis

Fever

Polydipsia

Abdominal pain

Hematochezia

<sup>\*</sup>Common clinical signs.

interfere with formation of chylomicrons, and damage intestinal mucosal cells. Diarrhea with malabsorption and steatorrhea may develop as a consequence. Findings on physical examination include lethargy, fever, dehydration, abdominal pain, and shock if blood loss is severe or ulcers have perforated. Potential abnormalities identified on a CBC include a regenerative anemia, hypoproteinemia, and neutrophilic leukocytosis. Abnormalities in the serum biochemistry panel include hypoproteinemia, hypoalbuminemia, hypocalcemia, and mild increases in serum alanine aminotransferase and alkaline phosphatase activities. Hyponatremia, hypochloremia, hypokalemia, and metabolic alkalosis may develop in dogs and cats that vomit frequently. Hyperglycemia and hypoglycemia have been noted in a few cases. The urinalysis is usually unremarkable.

Abdominal radiographs are usually normal. If an ulcer has perforated through the serosal surface, radiographic signs consistent with peritonitis may be present. Contrastenhanced radiographic studies may show gastric or duodenal ulcers; thickening of the gastric rugal folds, pyloric antrum, or intestine; and the rapid intestinal transit of barium. In an animal with concurrent severe esophagitis, secondary megaesophagus or aberrant, nonperistaltic esophageal motility may be identified fluoroscopically. Ultrasonographic evaluation of the abdomen may identify a pancreatic mass or its metastasis. However, gastrinomas vary tremendously in size and may not be detected with ultrasound.

Gastroduodenoscopy may reveal severe esophagitis and ulceration, especially near the cardia. Gastric rugal folds may be thickened. Gastric and duodenal hyperemia, erosions, or ulcerations are often visible. Histologic evaluation of esophageal, gastric, and duodenal biopsy specimens may be normal or may reveal variable degrees of inflammation consisting of infiltrates of lymphocytes, plasma cells and neutrophils, gastric mucosal hypertrophy, fibrosis, and loss of the mucosal barrier.

# **Diagnosis**

Gastrinoma should be included among the differential diagnoses for any dog or cat with melena or hematemesis or in which severe gastric and duodenal ulceration is identified. Unless a pancreatic mass is identified by ultrasonography, most dogs and cats with gastrinoma will inadvertently be diagnosed with severe inflammatory bowel disease, gastroduodenal erosions, and ulcers, and they will be treated with inhibitors of gastric acid secretion, mucosal protectants, antibiotics, and changes in diet. The probability of a gastrinoma increases if ultrasonography reveals a pancreatic mass, the dog or cat does not respond to medical therapy directed at nonspecific inflammation and ulceration of the gastrointestinal tract, or clinical signs and gastrointestinal tract ulceration recur after antiulcer therapy is discontinued. A definitive diagnosis of gastrinoma requires histologic and immunocytochemical evaluation of a pancreatic mass excised at surgery. Finding increased baseline serum gastrin concentrations from blood obtained after an overnight fast increases the suspicion of gastrinoma. Additional differential diagnoses for increased serum gastrin concentration include gastric outflow tract obstruction, renal failure, short-bowel syndrome, chronic gastritis, hepatic disease, and animals receiving antacid therapy (e.g., H<sub>2</sub>-receptor antagonists, proton pump inhibitors). Baseline serum gastrin concentrations may vary, with occasional values in the reference range in animals with gastrinoma. Provocative testing (e.g., secretin stimulation test, calcium challenge test) may be considered in dogs strongly suspected of having gastrinoma but with normal baseline serum gastrin concentrations. Exploratory laparotomy should also be considered. (See Suggested Readings for more information on provocative testing).

#### **Treatment**

Treatment should be directed at surgical excision of the tumor and control of gastric acid hypersecretion. Gastrointestinal tract ulceration can usually be managed by reducing gastric hyperacidity through the administration of H<sub>2</sub>-receptor antagonists (e.g., ranitidine, famotidine), proton pump inhibitors (e.g., omeprazole), gastrointestinal tract protectants (e.g., sucralfate), or prostaglandin E<sub>1</sub> analogs (e.g., misoprostol). (See Chapter 30 for more information on these gastrointestinal tract drugs.) Surgical resection of an ulcer may be required, especially if the ulcer has perforated the bowel. Surgical resection of the tumor is necessary to obtain a cure, although metastasis to the liver, regional lymph nodes, and mesentery is common. Even if metastatic disease is present, tumor debulking may enhance the success of medical therapy.

# **Prognosis**

The long-term prognosis for gastrinoma is guarded to poor. Evidence of metastasis was present in 76% of reported dogs and cats at the time a gastrinoma was diagnosed. Reported survival time in dogs and cats treated surgically, medically, or both ranged from 1 week to 18 months (mean, 4.8 months). However, the short-term prognosis has improved with the advent of drugs that can reduce gastric hyperacidity (e.g., ranitidine, famotidine) and protect and promote healing of the ulcers (e.g., sucralfate, misoprostol).

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#### DIABETIC KETOACIDOSIS

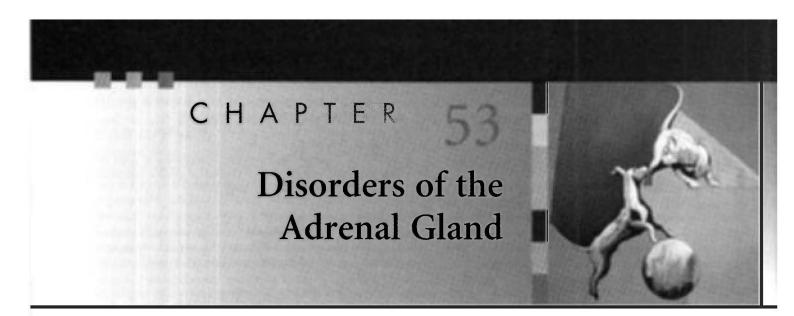
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# CHAPTER OUTLINE

# HYPERADRENOCORTICISM IN DOGS

Pituitary-Dependent Hyperadrenocorticism

Adrenocortical Tumors

Iatrogenic Hyperadrenocorticism

Signalment

Clinical Signs

Pituitary Macrotumor Syndrome

Medical Complications: Pulmonary

Thromboembolism

Clinical Pathology

Diagnostic Imaging

Tests of the Pituitary-Adrenocortical Axis

Mitotane

Trilostane

Ketoconazole

L-Deprenyl

Adrenalectomy

Radiation Therapy

# ATYPICAL CUSHING'S SYNDROME IN DOGS HYPERADRENOCORTICISM IN CATS

Clinical Signs and Physical Examination Findings

Clinical Pathology

Diagnostic Imaging

Tests of the Pituitary-Adrenocortical Axis

#### **HYPOADRENOCORTICISM**

Signalment

Clinical Signs and Physical Examination Findings

Clinical Pathology

Electrocardiography

Diagnostic Imaging

Therapy for Acute Addisonian Crisis

Maintenance Therapy for Primary Adrenal

Insufficiency

ATYPICAL HYPOADRENOCORTICISM

**PHEOCHROMOCYTOMA** 

INCIDENTAL ADRENAL MASS

# HYPERADRENOCORTICISM IN DOGS

# **Etiology**

Hyperadrenocorticism (Cushing's disease) is classified as pituitary dependent, adrenocortical dependent, or iatrogenic (i.e., resulting from excessive administration of glucocorticoids by the veterinarian or client).

# PITUITARY-DEPENDENT HYPERADRENOCORTICISM

Pituitary-dependent hyperadrenocorticism (PDH) is the most common cause of spontaneous hyperadrenocorticism, accounting for approximately 80% to 85% of cases. A functional adrenocorticotropic hormone (ACTH)-secreting pituitary tumor is found at necropsy in approximately 85% of dogs with PDH. Adenoma of the pars distalis is the most common histologic finding, with a smaller percentage of dogs diagnosed with adenoma of the pars intermedia and a few dogs diagnosed with functional pituitary carcinoma. Approximately 50% of dogs with PDH have pituitary tumors less than 3 mm in diameter, and most of the remaining dogs, specifically those without central nervous system (CNS) signs, have tumors 3 to 10 mm in diameter at the time PDH is diagnosed. Approximately 10% to 20% of dogs have pituitary tumors (i.e., macrotumors) exceeding 10 mm in diameter at the time PDH is diagnosed. These tumors have the potential to compress or invade adjacent structures and cause neurologic signs as they expand dorsally into the hypothalamus and thalamus (Fig. 53-1).

Excessive secretion of ACTH causes bilateral adrenocortical hyperplasia and excess cortisol secretion from the adrenal cortex (Fig. 53-2). Because normal feedback inhibition of ACTH secretion by cortisol is missing, excessive ACTH secretion persists despite increased adrenocortical secretion of cortisol. Episodic secretion of ACTH and cortisol is common and results in fluctuating plasma concentrations that may at times be within the reference range.

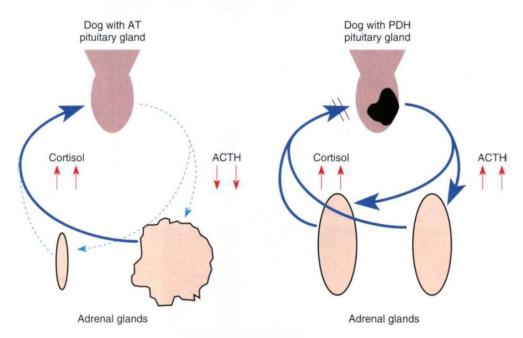
#### ADRENOCORTICAL TUMORS

Adrenocortical tumors (ATs) account for the remaining 15% to 20% of dogs with spontaneous hyperadrenocorticism.



#### FIG 53-1

**A**, A 10-year-old male castrated mixed-breed dog with pituitary-dependent hyperadreno-corticism. Initial clinical signs of polyuria, polydipsia, and endocrine alopecia progressed to severe stupor, anorexia, adipsia, weight loss, and loss of body temperature regulation. **B**, Cross-section of the brain from the dog in **A** showing a pituitary macroadenoma that is severely compressing the surrounding brain structures.



#### FIG 53-2

The pituitary-adrenocortical axis in dogs with a functioning adrenocortical tumor (AT; *left*) and in dogs with pituitary-dependent hyperadrenocorticism (PDH; *right*). Excess cortisol secretion from an AT causes pituitary suppression, decreased plasma adrenocorticotropic hormone (ACTH) concentration, and atrophy of the contralateral adrenal gland. Dogs with PDH have excess ACTH secretion, usually from a functional pituitary adenoma, which causes bilateral adrenomegaly and excess plasma cortisol concentrations.

Adrenocortical adenoma and carcinoma occur with equal frequency. There are no consistent clinical or biochemical features that help distinguish dogs with functional adrenal adenomas from those with adrenal carcinomas, although carcinomas tend to be larger than adenomas on abdominal ultrasound. Adrenocortical carcinomas may invade adjacent structures (e.g., phrenicoabdominal vein, caudal vena cava, kidney) or metastasize to the liver and lung.

Bilateral ATs can occur in dogs but are rare. A nonfunctional AT or an AT causing hyperadrenocorticism and a pheochromocytoma in the contralateral gland is a more common cause of bilateral adrenal masses in dogs. Macronodular hyperplasia of the adrenals has also been identified in dogs. The adrenals in such animals are usually grossly enlarged, with multiple nodules of varying sizes within the adrenal cortex. The exact pathogenesis of this latter syn-

drome is unclear, although most cases in dogs are presumed to represent an anatomic variant of PDH. Increased plasma 17-OH-progesterone concentrations have also been documented in dogs with an adrenal mass and clinical manifestations of hyperadrenocorticism but normal plasma cortisol concentrations after administration of ACTH or dexamethasone (see the section on atypical Cushing's syndrome, p. 830).

Adrenocortical tumors causing hyperadrenocorticism (ATHs) are autonomous and functional and randomly secrete excessive amounts of cortisol independent of pituitary control. The cortisol produced by these tumors suppresses circulating plasma ACTH concentrations, causing cortical atrophy of the uninvolved adrenal and atrophy of all normal cells in the involved adrenal (see Fig. 53-2). This atrophy creates asymmetry in the size of the adrenal glands, which can be identified by abdominal ultrasonography. Most, if not all, of these tumors appear to retain ACTH receptors and respond to administration of exogenous ACTH. ATHs are typically unresponsive to manipulation of the hypothalamic-pituitary axis with glucocorticoids such as dexamethasone.

#### IATROGENIC HYPERADRENOCORTICISM

Iatrogenic hyperadrenocorticism typically results from the excessive administration of glucocorticoids to control allergic or immune-mediated disorders. It can also develop as a result of the administration of eye, ear, or skin medications containing glucocorticoids, especially in small dogs (weight less than 10 kg) receiving them long term. Because the hypothalamic-pituitary-adrenocortical axis is normal, the prolonged excessive administration of glucocorticoids suppresses circulating plasma ACTH concentrations, causing bilateral adrenocortical atrophy. In these animals ACTH stimulation test results are consistent with spontaneous hypoadrenocorticism despite clinical signs of hyperadrenocorticism.

#### Clinical Features

#### **SIGNALMENT**

Hyperadrenocorticism typically develops in dogs 6 years of age and older (median age 10 years) but has been documented in dogs as young as 1 year. There is no apparent sex-related predisposition, although AT appears to be diagnosed more commonly in female dogs. PDH and ATH have been diagnosed in numerous breeds. All Poodle breeds, Dachshunds, various Terrier breeds, German Shepherd Dogs, Beagles, and Labrador Retrievers are commonly represented, and Boxers and Boston Terriers appear to be at increased risk for PDH. PDH tends to occur more frequently in smaller dogs; 75% of dogs with PDH weigh less than 20 kg. Approximately 50% of dogs with functional ATH weigh more than 20 kg.

#### **CLINICAL SIGNS**

The most common clinical signs are polyuria, polydipsia, polyphagia, panting, abdominal enlargement, endocrine alo-

pecia, mild muscle weakness, and lethargy (Fig. 53-3; Table 53-1). Most dogs exhibit several, but not all, of these clinical signs. The more signs evident in the history, the greater the index of suspicion for hyperadrenocorticism. Additional findings on physical examination (see Table 53-1) help establish the diagnosis.

Dogs are occasionally seen because of isolated polyuria and polydipsia, bilaterally symmetric endocrine alopecia, or panting. There may be no other historic or physical examination findings consistent with hyperadrenocorticism. The diagnosis of hyperadrenocorticism is not readily apparent in these dogs. Fortunately, hyperadrenocorticism is a differential diagnosis for polyuria and polydipsia, endocrine alopecia, and panting and will be identified as the clinician works through the differentials for these problems. Similarly, hyperadrenocorticism causes insulin resistance and can lead to the development of diabetes mellitus. Clinical signs (other than polyuria and polydipsia) and physical examination findings suggestive of hyperadrenocorticism are often missing in diabetic dogs with concurrent hyperadrenocorticism. A clinical suspicion for hyperadrenocorticism develops after critical evaluation of routine blood test results (e.g., increased serum alkaline phosphatase [ALP] activity, isosthenuric urine) or after resistance to insulin treatment is identified.



**CLINICAL SIGNS** 

**TABLE 53-1** 

Clinical Signs and Physical Examination Findings in Dogs with Hyperadrenocorticism

Polyuria, polydipsia*
Polyphagia*
Panting*
Abdominal enlargement*
Endocrine alopecia*
Weakness*
Lethargy
Calcinosis cutis
Cutaneous
hyperpigmentation
Neurologic signs (PMA)
Stupor
Ataxia
Circling
Aimless wandering
Pacing
Behavioral alterations
Respiratory distress-dyspnea

Endocrine alopecia\* Epidermal atrophy\* Comedones\* Cutaneous hyperpigmentation\* Calcinosis cutis Abdominal enlargement\* Hepatomegaly\* Muscle wasting\* Bruising Testicular atrophy Failure to cycle (intact female) Neurologic signs (PMA) Dyspnea (pulmonary thromboemboli) Facial nerve paralysis Myotonia

PHYSICAL EXAMINATION

**FINDINGS** 

Stiff gait (myotonia)

(pulmonary thromboemboli)

<sup>\*</sup> Common findings.
PMA, Pituitary macroadenoma.



#### FIG 53-3

**A**, A 1-year-old male Miniature Poodle with pituitary-dependent hyperadrenocorticism (PDH). Note the truncal distribution of the endocrine alopecia with the pot-bellied appearance. **B**, A 9-year-old male castrated mixed-breed dog with PDH. Note the severe laxity of the ligaments, resulting in hyperextension of the carpal ligaments and ambulation on the hocks. A "rat tail" has also developed and is a finding also associated with hypothyroidism. **C**, An 8-year-old male castrated Chihuahua with PDH. Note the pot-bellied appearance and severe calcinosis cutis. **D**, A 7-year-old Standard Poodle with PDH. The primary owner complaints at presentation were polyuria, polydipsia, and progressively worsening symmetric endocrine alopecia. **E**, An adult mixed-breed dog with PDH. The primary owner complaints were polyuria, polydipsia, excessive panting, and severe weakness of the rear limbs. Note the absence of hair growth on the ventral abdomen, which had been shaved for an abdominal ultrasound 2 months before presentation.

В

# FIG 53-4

**A,** Postgadolinium administration magnetic resonance imaging (MRI) scan of a 9-year-old male castrated German Shepherd Dog with pituitary-dependent hyperadrenocorticism (PDH) and a pituitary mass (arrow). There were no neurologic signs present at the time the MRI scan was performed. **B,** Postgadolinium administration MRI scan of an 8-year-old Boston Terrier with PDH, a large pituitary mass invading the brainstem, and signs of disorientation, ataxia, and circling. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, St Louis, 2004, WB Saunders.)

PHILIPS GYROSCAN S15

#### PITUITARY MACROTUMOR SYNDROME

Neurologic signs may develop in dogs with PDH as a result of expansion of the pituitary tumor into the hypothalamus and thalamus (see Fig. 53-1). Neurologic signs may be present at the time PDH is diagnosed but usually develop 6 months or longer after PDH is identified. The most common neurologic sign is a dull, listless attitude (i.e., stupor). Additional signs of pituitary macroadenoma include inappetence, aimless wandering, pacing, ataxia, head pressing, circling, and behavioral alterations. In the event of severe compression of the hypothalamus, abnormalities related to dysfunction of the autonomic nervous system develop, including adipsia, loss of temperature regulation, erratic heart rate, and inability to be roused from a sleeplike state. Identification of a pituitary macrotumor requires computed tomography (CT) or magnetic resonance imaging (MRI; Fig. 53-4). There are no biochemical or endocrine test results that reliably correlate with the size of the pituitary tumor.

# MEDICAL COMPLICATIONS: PULMONARY THROMBOEMBOLISM

Several medical complications can develop secondary to prolonged cortisol excess (Box 53-1). The most worrisome is pulmonary thromboembolism (PTE), which generally occurs in dogs undergoing adrenalectomy for AT. Thromboemboli may also affect the kidney, gastrointestinal tract, heart, and CNS. There is no apparent correlation between control of hyperadrenocorticism and development of thromboemboli. Factors predisposing to the development of PTE in dogs with hyperadrenocorticism include inhibition of fibrinolysis (corticosteroids stimulate the release of plasminogen activator inhibitors), systemic hypertension, protein-losing glomerulonephropathy, decreased serum antithrombin III concentrations, increased concentrations of several coagulation



BOX 53-1

Medical Complications Associated with Hyperadrenocorticism in Dogs

Systemic hypertension Pyelonephritis

Cystic calculi (calcium phosphate, oxalate)

Glomerulonephropathy, proteinuria

Congestive heart failure

Pancreatitis

Diabetes mellitus

Pulmonary thromboembolism

Pituitary macrotumor syndrome

factors, and an increased hematocrit value. Clinical signs of PTE include acute respiratory distress; orthopnea; and, less commonly, a jugular pulse. Thoracic radiographs may reveal no abnormalities, or they may show hypoperfusion, alveolar pulmonary infiltrates, or a pleural effusion. There may be an increased diameter and blunting of the pulmonary arteries, absence of perfusion of the obstructed pulmonary vasculature, and overperfusion of the unobstructed pulmonary vasculature. Normal thoracic radiograph findings in a dyspneic dog that does not have a large airway obstruction suggest a diagnosis of PTE. Arterial blood gas analysis typically reveals a decrease in the partial pressures of arterial oxygen and carbon dioxide, and mild metabolic acidosis. Thrombosis may be confirmed by angiography of the lungs or by radionuclear lung scanning. Therapy consists of general supportive care, oxygen, anticoagulants, and time (see Chapter 12). The prognosis for dogs with PTE is guarded to grave. If dogs do recover, it typically takes 5 to 10 days before they can be safely removed from oxygen support.

# Diagnosis

A thorough evaluation should be done in any dog suspected of having hyperadrenocorticism and should include a complete blood count (CBC); serum biochemistry panel; urinalysis with bacterial culture; and, if available, abdominal ultrasonography. Results of these tests will increase or decrease the index of suspicion for hyperadrenocorticism; identify common concurrent problems (e.g., urinary tract infection); and, in the case of ultrasonography, provide valuable information for localizing the cause of the disorder (i.e., PDH versus AT). Endocrine studies required to confirm the diagnosis and localize the cause of the disorder can then be performed.

## **CLINICAL PATHOLOGY**

Common clinicopathologic alterations caused by hyperadrenocorticism are listed in Box 53-2. An increase in ALP activity and cholesterol concentration is the most reliable indicator of hyperadrenocorticism. The major contributor to increased serum ALP is the corticosteroid-induced isoenzyme of ALP derived from the bile canalicular membrane of hepatocytes. Approximately 85% of dogs with hyperadrenocorticism have ALP activities that exceed 150 IU/L; values in excess of 1000 IU/L are common, and values in excess of 10,000 IU/L are occasionally identified. There is no correlation between the magnitude of increase in serum ALP activity and the severity of hyperadrenocorticism, response to therapy, or prognosis. There is also no correlation between the magnitude of increase in serum ALP activity and hepatocellular death or hepatic failure. The ALP activity can be normal in some dogs with hyperadrenocorticism, and an increase in ALP activity by itself is not diagnostic for hyperadrenocorticism. Similarly, an increase in the activity of the corticosteroid-induced isoenzyme of alkaline phosphatase (SIAP) is not a finding specific to hyperadrenocorticism or exogenous glucocorticoid administration; an increase in SIAP activity occurs commonly with many disorders, including diabetes mellitus, primary hepatopathies, pancreatitis,



BOX 53-2

Clinicopathologic Abnormalities Commonly Identified in Dogs with Hyperadrenocorticism

Neutrophilic leukocytosis
Eosinopenia
Lymphopenia
Mild erythrocytosis
Increased alkaline phosphatase activity
Increased alanine aminotransferase activity
Hypercholesterolemia
Lipemia
Hyperglycemia
Hyposthenuria, isosthenuria
Urinary tract infection
Proteinuria
Mild increase in pre- and postprandial bile acids

congestive heart failure, and neoplasia as well as in dogs receiving certain drugs (e.g., anticonvulsants). However, finding no SIAP in the serum may be of diagnostic value in ruling out hyperadrenocorticism.

Urine specific gravity is typically less than 1.020 in dogs with hyperadrenocorticism that have free access to water. Water-deprived hyperadrenal dogs maintain the ability to concentrate urine, although usually the concentrating ability remains less than normal. As such, urine specific gravities of 1.025 to 1.035 may be identified if urine is obtained after water has been withheld from the dog.

Proteinuria is a common finding in dogs with untreated hyperadrenocorticism. Proteinuria may be caused by glucocorticoid-induced systemic and glomerular hypertension, glomerulonephritis, or glomerulosclerosis. Urine protein: creatinine ratios are usually less than 4, although values in excess of 8 have been identified. Proteinuria decreases and often resolves in response to treatment of hyperadrenocorticism.

Urinary tract infection is a common sequela of hyperadrenocorticism. Hyposthenuria and the antiinflammatory effects of glucocorticoids commonly interfere with the identification of bacteria or inflammatory cells in the urine. Whenever hyperadrenocorticism is suspected, antepubic cystocentesis with bacterial culture of the urine and antibiotic sensitivity testing is strongly recommended, regardless of the urinalysis findings.

#### DIAGNOSTIC IMAGING

Abnormalities identified by thoracic and abdominal radiography and by abdominal ultrasonography are listed in Box 53-3. The most consistent radiographic findings in dogs with hyperadrenocorticism are enhanced abdominal contrast secondary to increased fat distribution in the abdomen; hepatomegaly caused by steroid hepatopathy; an enlarged urinary bladder secondary to the polyuric state; and dystrophic calcification of the trachea, bronchi, and occasionally the skin and abdominal blood vessels. The most important but least common radiographic finding is a soft-tissue mass or calcification in the area of an adrenal gland (Fig. 53-5). These findings are suggestive of an adrenal tumor. Approximately 50% of ATH are calcified; the frequency of calcification is equally distributed between adenoma and carcinoma. Metastasis of an adrenocortical carcinoma to the pulmonary parenchyma is occasionally evident on thoracic radiographs.

Abdominal ultrasonography is used to evaluate the size and shape of the adrenals and to search for additional abnormalities in the abdomen (e.g., cystic calculi, tumor thrombus; Fig. 53-6). Finding bilaterally symmetric normal-size or large adrenals (defined as having a maximum width greater than 0.8 cm) in a dog with hyperadrenocorticism is evidence for adrenal hyperplasia caused by PDH. The adrenal glands in dogs with PDH are similar but not exactly the same in size and shape; should have smooth, not irregular borders; can exceed 2 cm in maximum width; may have a bulbous cranial or caudal pole; and do not invade surrounding blood vessels or organs (see Fig. 53-6). An AT is typically identified as an



BOX 53-3

Abnormalities Identified by Abdominal and Thoracic Radiography and Abdominal Ultrasonography in Dogs with Hyperadrenocorticism

#### **Abdominal Radiographs**

Excellent abdominal detail

Hepatomegaly\*

Distention of urinary bladder\*

Cystic calculi

Adrenal mass

Calcified adrenal gland

Dystrophic calcification of soft tissues, calcinosis cutis

Osteoporosis of vertebrae

#### Thoracic Radiographs

Calcification of trachea and bronchi\*

Osteoporosis of vertebrae

Pulmonary metastases from adrenocortical carcinoma

Pulmonary thromboembolism

Hypovascular lung fields

Alveolar infiltrates

Enlarged right pulmonary artery

Right-sided cardiomegaly

Pleural effusion

#### **Abdominal Ultrasonography**

Bilateral adrenomegaly (PDH)\*

Adrenal mass (ATH)

Tumor thrombus (ATH)

Hepatomegaly\*

Hyperechogenic liver\*

Distention of urinary bladder

Cystic calculi

Calcification of adrenal gland (ATH)

Dystrophic calcification of soft tissues

PDH, Pituitary-dependent hyperadrenocorticism; ATH, adrenocortical tumor causing hyperadrenocorticism.

\* Common findings.



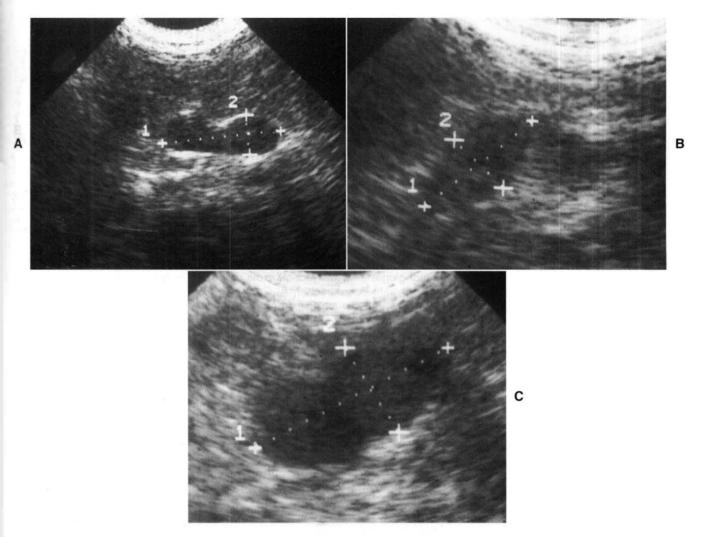
FIG 53-5

**A,** Lateral radiograph from a dog with adrenal-dependent hyperadrenocorticism showing a calcified adrenal mass cranial to the kidney (arrow). **B,** Ventrodorsal radiograph from a dog with adrenal-dependent hyperadrenocorticism showing a calcified adrenal mass craniomedial to the kidney and lateral to the spine (arrow). Compression of the abdomen in the region of the adrenal gland with a paddle has enhanced radiographic contrast, allowing better visualization of the adrenal mass.

adrenal mass (Fig. 53-7). Size is quite variable, ranging from 1.5 to greater than 8 cm in maximum width. Small adrenal masses (i.e., less than 3 cm in maximum width) often maintain a smooth contour and may distort only a portion of the adrenal gland; one or both poles of the adrenal gland may still appear normal. With large adrenal masses (typically greater than 3 cm in maximum width), the adrenal gland usually becomes distorted and unrecognizable, the contour of the gland becomes irregular, and compression and/or

invasion into adjacent blood vessels and organs may occur (Fig. 53-8). These changes suggest adrenocortical carcinoma. Identification of calcification within the mass does not differentiate adenoma from carcinoma. Generally, the larger the mass, the more likely it is carcinoma. Asymmetry in the size of the adrenal glands is evident (see Fig. 53-2). Ideally, the contralateral unaffected adrenal should be small or undetectable (maximum width typically less than 0.3 cm) as a result of AT-induced adrenocortical atrophy (see Fig. 53-7),

Р



#### FIG 53-6

Ultrasound images of the adrenal gland in three dogs with pituitary-dependent hyperadre-nocorticism (PDH) illustrating the differences in size and shape of the adrenal gland that can occur with PDH. **A,** The adrenal gland in this dog has maintained the typical kidney-bean shape often identified in normal dogs. However, the maximum diameter of the gland was enlarged at 0.85 cm. The contralateral adrenal gland was similar in size and shape. **B,** The adrenal gland in this dog is uniformly thickened and appears plump rather than kidney-bean shaped. The maximum diameter of the gland was 1.2 cm. The contralateral adrenal gland was similar in size and shape. **C,** Although the adrenal gland has maintained some semblance of a kidney-bean shape in this dog, the gland has undergone marked enlargement, with a maximum diameter of 2.4 cm. The contralateral adrenal gland was similar in size and shape.

although a normal-size contralateral adrenal gland does not rule out hyperadrenocorticism caused by AT. Identification of an adrenal mass and a normal-to-large contralateral adrenal gland in a dog with clinical signs supportive of hyperadrenocorticism suggests the possibility of PDH and a concurrent adrenal mass that may be a pheochromocytoma, a functional adrenocortical tumor, or a nonfunctional AT (Fig. 53-9). Finding normal-size adrenal glands in a dog with confirmed hyperadrenocorticism is most consistent with a diagnosis of PDH. Finding bilateral adrenomegaly with the appearance of multiple nodules of varying size is suggestive

of macronodular hyperplasia (Fig. 53-10). Bilateral adrenal macronodular hyperplasia is believed to represent an anatomic variant of PDH. Failure to identify either adrenal is considered an inconclusive finding, and ultrasonography should be repeated at a later time.

CT and MRI can be used to evaluate the pituitary gland for a macroadenoma and assess the size and symmetry of the adrenal glands. Contrast enhancement using an iodinated contrast agent (CT) or gadolinium (MRI) given by continuous intravenous (IV) infusion during the imaging procedure aids in the identification of a pituitary macroad-

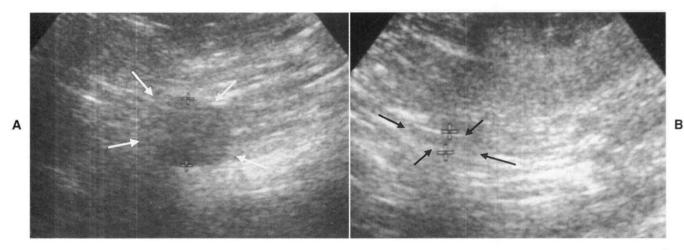


FIG 53-7

Ultrasound images of the adrenal glands in an 11-year-old male castrated Golden Retriever with adrenal-dependent hyperadrenocorticism. **A,** Cortisol-secreting tumor affecting the right adrenal gland (*arrows*). The maximum diameter of the adrenal mass was 1.6 cm. **B,** The left adrenal gland has undergone marked atrophy (*arrows* and *crosses*) as a result of suppression of pituitary adrenocorticotropic hormone secretion after negative feedback inhibition caused by the adrenocortical tumor. The maximum diameter of the left adrenal gland was less than 0.2 cm.

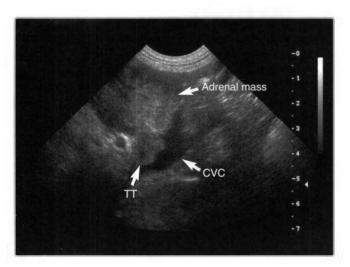


FIG 53-8

Ultrasound image of a mass affecting the left adrenal gland (adrenal mass) and extending into the lumen of the caudal vena cava (CVC) creating a tumor thrombus (TT) in a 9-year-old male Standard Poodle. The maximum width of the adrenal mass was 3.8 cm. The histopathologic diagnosis was pheochromocytoma.

enoma and the adrenal glands during CT and MRI examination, respectively (see Fig. 53-4). The primary indications for CT or MRI are to confirm the presence of a visible pituitary tumor in a dog with clinical signs suggestive of macrotumor (see the section on pituitary macrotumor syndrome, p. 814) or in dogs diagnosed with PDH in which the client is willing to consider radiation treatment should a pituitary mass be

identified (see the section on radiation therapy, p. 829) and to assess the size of an adrenal mass and extent of infiltration of the mass into surrounding blood vessels and organs before adrenalectomy. MRI is superior to CT in detecting small pituitary tumors; in detecting associated tumor features such as edema, cysts, hemorrhage, and necrosis; and in imaging the adrenal glands.

# TESTS OF THE PITUITARY-ADRENOCORTICAL AXIS

The clinical signs, physical examination findings, and clinicopathologic alterations usually establish a presumptive diagnosis of hyperadrenocorticism, and results of an abdominal ultrasound provide valuable information regarding probable location of the lesion. Tests to establish the diagnosis of hyperadrenocorticism include the urine cortisol: creatinine ratio (UCCR), the ACTH stimulation test, the low-dose dexamethasone suppression (LDDS) test, and the oral dexamethasone suppression test (Table 53-2). Baseline serum cortisol measurement by itself is of no diagnostic value in diagnosing hyperadrenocorticism. Discriminatory tests are used to identify the etiology (i.e., PDH versus AT) in dogs with confirmed hyperadrenocorticism and include the low- and high-dose dexamethasone suppression test and baseline endogenous ACTH concentration. The most commonly used tests in our hospital are the UCCR, LDDS test, and abdominal ultrasound. An endogenous ACTH concentration is evaluated when abdominal ultrasound suggests an adrenal mass but results of the LDDS test are inconclusive or suggest PDH and when an adrenal mass is identified with contralateral adrenomegaly.

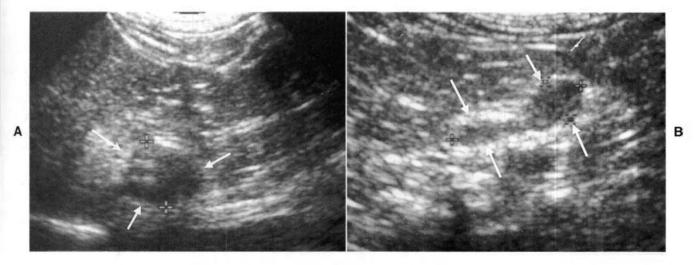


FIG 53-9

Ultrasound images of the adrenal glands in a 10-year-old female spayed Bichon Frise presented for acute onset of vomiting. **A**, An unexpected mass involving the right adrenal gland, measuring 1.4 cm in maximum diameter, was identified (arrows). **B**, The left adrenal gland was normal in size and shape (arrows); the maximum diameter was 0.6 cm. The normal-size left adrenal gland suggests that the right adrenal mass is either a pheochromocytoma or is nonfunctional. Results of routine blood work and tests for hyperadrenocorticism were normal.

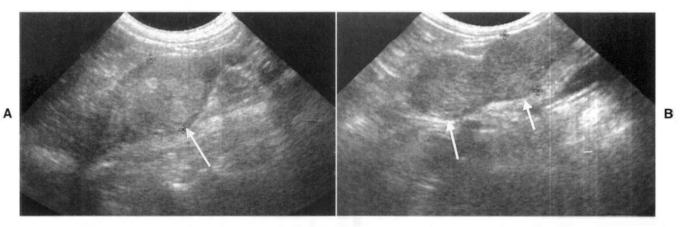


FIG 53-10

Ultrasound images of the adrenal glands (arrows) in an 11-year-old female spayed Shih Tzu. The right adrenal gland (A) measured 1.8 cm in maximum diameter and had a nodular echogenic pattern. In contrast, the left adrenal gland (B) had a large nodule located in each pole of the gland; each measured approximately 1.4 cm in maximum diameter. Tests of the pituitary-adrenocortical axis were diagnostic for pituitary-dependent hyperadrenocorticism; this finding, in conjunction with the findings on ultrasound, suggests macronodular hyperplasia of the adrenal glands.

False-positive and false-negative test results occur with all of the diagnostic tests for hyperadrenocorticism. When the results are unexpected or questionable, another diagnostic test can be performed or the same diagnostic test repeated, preferably after waiting several months. Occasionally, results of different diagnostic tests performed in the same dog are contradictory. The decision to perform discriminatory tests or to initiate therapy should depend on the clinician's index of suspicion for the disease formulated from a review of the history, findings on physical examination, and

results of diagnostic tests. If there is doubt or uncertainty about the diagnosis, therapy for hyperadrenocorticism should be withheld and the dog reevaluated several months later.

#### **Urine Cortisol: Creatinine Ratio**

The UCCR is an excellent initial screening test for hyperadrenocorticism in dogs. Ideally, the UCCR should be determined from free-catch urine samples obtained by the client in the nonstressful home environment. The stress associated

TABLE 53-2

# Diagnostic Tests to Assess the Pituitary-Adrenocortical Axis in Dogs with Suspected Hyperadrenocorticism

TEST	PURPOSE	PROTOCOL	RESULTS		INTERPRETATION	
Urine cortisol: creatinine ratio	Rule out Cushing's syndrome	Urine collected at home	Normal		Not supportive of Cushing's syndrome	
			Incre	eased	Additional tests for Cushing's indicated	
			4-hr post-dexamethasone:	8-hr post-dexamethasone:	-	
Low-dose	Diagnose Cushing's	0.01 mg dexamethasone/kg IV;	_ ′	<1.5 μg/dl	Normal	
dexamethasone	syndrome and	serum pre- and 4- and 8-hr post-	<1.5 μg/dl	>1.5 μg/dl	PDH	
suppression test	differentiate PDH	dexamethasone	<50% of pre-value	>1.5 μg/dl	PDH	
сорруковичи хоси	from ATH		_	>1.5 µg/dl and <50% of pre-value	PDH	
			>1.5 µg/dl and >50% of pre-value	>1.5 μg/dl	PDH or ATH	
ACTH stimulation	Diagnose Cushing's	2.2 IU ACTH gel*/kg IM; serum pre-	Post-ACTH cortisol concentration:		Strongly suggestive†	
	syndrome	and 2-hr post-ACTH	>24 μg/dl		Suggestive‡	
	,	or	19-24 μg/dl		Normal	
		0.25 mg of synthetic ACTH*/dog IM; serum pre- and 1-hr post-ACTH	8-18 μg/dl <8 μg/dl		latrogenic Cushing's syndrome	
High-dose	Differentiate PDH	0.1 mg of dexamethasone/kg IV;	Post-dexamethasone cortisol concentration:		PDH	
dexamethasone	from ATH	serum pre- and 8-hr post-	construction < 50% of pre-value		PDH	
	IIOIII AITT	dexamethasone			PDH or ATH	
suppression test	dexamernasone		<1.5 µg/dl >50% of pre-value		PDITOLATII	
O   -   -	Differentiate PDH	Heima annuala fan HCCR an 2	Post-dexamethasone UCCR value:		PDH	
Oral dexamethasone		Urine sample for UCCR on 2			PDH or ATH	
suppression test	from ATH	consecutive mornings, then 0.1 mg of dexamethasone/kg per os q8h for 3 treatments, then urine sample for UCCR the following morning	<50% of baseline value** ≥50% of baseline value		PULL OF AIT	
Endogenous ACTH	Differentiate PDH	Plasma sample obtained between 8-	<2 p	mol/L	ATH	
Ŭ	from ATH	10 A.M.		omol/L	Nondiagnostic	
		Special handling required		omol/L	PDH	

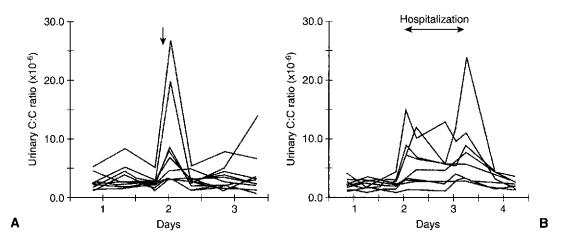
PDH, Pituitary-dependent hyperadrenocorticism; ATH, adrenocortical tumor-dependent hyperadrenocorticism; IV, intravenous; ACTH, adrenocorticotropic hormone; IM, intramuscular; UCCR, urine cortisol; creatinine ratio.

<sup>\*</sup> ACTH gel: Acthar Gel, Questcor Pharmaceuticals; synthetic ACTH: Cortrosyn, Amphastar Pharmaceuticals.

<sup>\*\*</sup> Baseline value is the mean of two UCCR values obtained before dexamethasone administration.

<sup>†</sup>Strongly suggestive of hyperadrenocorticism.

<sup>‡</sup> Suggestive of hyperadrenocorticism.



Urinary corticoid: creatinine (C:C) ratio measured in 12 pet dogs before and after a visit to a referral clinic for orthopedic examination (A) and in 9 healthy pet dogs before, during, and after a 1.5-day hospitalization at a referral clinic (B). The arrows indicate time of visit to the referral clinic. Note the increase in the urinary C:C ratio in a few dogs affiliated with a visit to a veterinary practice. (From van Vonderen IK et al: Influence of veterinary care on the urinary corticoid:creatinine ratio in dogs, J Vet Intern Med 12:431, 1998.)

with driving the dog to the veterinary hospital and having the dog undergo a physical examination before collecting urine can increase the test results (Fig. 53-11). The UCCR is increased in dogs with hyperadrenocorticism compared with healthy dogs. Normal UCCR test results can occur in dogs with hyperadrenocorticism but are uncommon. Unfortunately, the specificity of the UCCR is only 20% in dogs. The UCCR is often increased in dogs with nonadrenal illness and in dogs with clinical signs consistent with hyperadrenocorticism but with a normal pituitary-adrenocortical axis (Fig. 53-12). A normal UCCR is a strong finding against hyperadrenocorticism and can be used as a screening test for normalcy; however, an increased UCCR is not diagnostic of hyperadrenocorticism. Additional tests are indicated when the UCCR is increased or when the UCCR is normal but the clinical picture strongly suggests hyperadrenocorticism.

# Low-Dose Dexamethasone Suppression Test

In the normal dog relatively small doses of dexamethasone given intravenously can inhibit pituitary secretion of ACTH, causing a prolonged decline in the serum cortisol concentration (Fig. 53-13). Dexamethasone is used because it does not interfere with the radioimmunoassays used to measure cortisol. The abnormal pituitary in dogs with PDH is somewhat resistant to the negative feedback action of dexamethasone, and the metabolic clearance of dexamethasone may be abnormally accelerated as well. The administration of a small dose of dexamethasone to a dog with PDH causes the serum cortisol concentration to be variably suppressed; however, it is no longer suppressed by 8 hours after dexamethasone administration, compared with the response seen in normal dogs. ATH function independently of ACTH control, and dexamethasone does not affect the serum cortisol concentration, regardless of the dose or time of blood

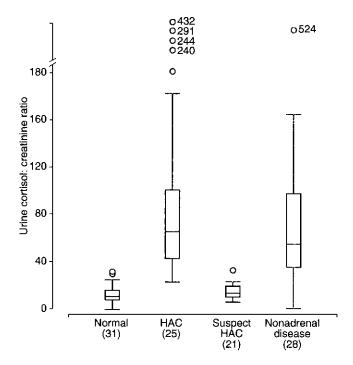
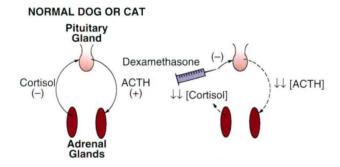
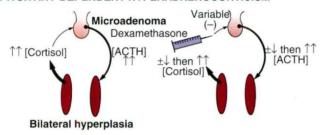


FIG 53-12

Box plots of the urine cortisol: creatinine ratios found in normal dogs, dogs with hyperadrenocorticism (HAC), dogs in which hyperadrenocorticism was initially suspected but that did not have the disease (suspect HAC), and dogs with a variety of severe, nonadrenal diseases. For each box plot, T-bars represent the main body of data, which in most instances are equal to the range. Each box represents an interquartile range (twenty-fifth to seventy-fifth percentile). The horizontal bar in each box is the median. Open circles represent outlying data points. Numbers in parentheses indicate the numbers of dogs in each group. (From Smiley LE et al: Evaluation of a urine cortisol: creatinine ratio as a screening test for hyperadrenocorticism in dogs, J Vet Intern Med 7:163, 1993.)



#### PITUITARY-DEPENDENT HYPERADRENOCORTICISM



# ADRENOCORTICAL NEOPLASIA Dexamethasone (-) [ACTH] | (ACTH) | (A

#### FIG 53-13

Adrenal tumor

Effects of dexamethasone administration on the pituitary-adrenocortical axis in healthy dogs or cats and in dogs or cats with either pituitary-dependent hyperadrenocorticism (PDH) or adrenocortical neoplasia. In PDH dexamethasone may initially suppress pituitary adrenocorticotropic hormone (ACTH) secretion, but the suppression is short-lived. The plasma cortisol concentrations initially decline but increase above normal within 2 to 6 hours of dexamethasone administration. In adrenocortical neoplasia pituitary ACTH secretion is already suppressed; thus dexamethasone has no effect.

sampling because pituitary corticotrophs are already suppressed and blood ACTH concentration is undetectable.

The LDDS test is a reliable diagnostic test for differentiating normal dogs from those with hyperadrenocorticism and may identify PDH. Sensitivity and specificity are approximately 90%. The LDDS does not identify iatrogenic hyperadrenocorticism, nor is it used to assess a dog's response to mitotane (lysodren) or trilostane therapy. A normal or inconclusive LDDS test result does not by itself rule out hyperadrenocorticism. If hyperadrenocorticism is suspected, additional tests of the pituitary-adrenocortical axis should be performed. Similarly, an abnormal LDDS test result does not by itself confirm hyperadrenocorticism. Results of the LDDS test may be affected by concurrently administered

anticonvulsant drugs, stress, excitement, exogenous glucocorticoids, and nonadrenal disease; the more severe the nonadrenal disease, the more likely the LDDS test result will be falsely positive. When performing the LDDS test, the clinician must ensure that all stressors are kept to a minimum; other procedures should not be performed until the test is completed, and the effect of concurrent clinical problems should be considered when interpreting results.

The protocol for the LDDS test and interpretation of results are described in Table 53-2. The clinician may use either dexamethasone sodium phosphate or dexamethasone in polyethylene glycol. The 8-hour postdexamethasone serum cortisol concentration is used to confirm hyperadrenocorticism. Normal dogs typically have serum cortisol values less than 1.0 g/dl, whereas dogs with PDH and AT have serum cortisol concentrations greater than 1.5 | g/dl 8 hours after dexamethasone administration. In general, the higher the 8-hour postdexamethasone serum cortisol concentration is above 1.5 µ g/dl, the more supportive the test result is for hyperadrenocorticism. Cortisol concentrations between 1.0 and 1.5 µ g/dl are nondiagnostic. If results are in the nondiagnostic range, the clinician must rely on other information, including other tests of the pituitary-adrenocortical axis, to determine if hyperadrenocorticism is the correct diagnosis.

If the 8-hour postdexamethasone serum cortisol value supports a diagnosis of hyperadrenocorticism, the 4-hour serum cortisol value may then be of value in identifying PDH. Low doses of dexamethasone suppress pituitary ACTH secretion and serum cortisol concentrations in approximately 60% of dogs with PDH. Suppression does not occur in dogs with AT, nor does it occur in approximately 40% of dogs with PDH. Suppression is defined as a 4-hour postdexamethasone serum cortisol concentration of less than 1.5 | g/ dl, a 4-hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration, or an 8hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration. Any dog with hyperadrenocorticism that meets one or more of these criteria most likely has PDH. If none of these criteria is met, then results of the LDDS test are consistent with lack of suppression but not informative in terms of whether it is pituitary or adrenal in origin. Differentiation between PDH and AT must rely on results of abdominal ultrasound, the HDDS test, or plasma endogenous ACTH concentration.

# **Oral Dexamethasone Suppression Test**

An alternative at-home oral dexamethasone suppression test has been used for years at the University of Utrecht, The Netherlands. This test relies entirely on results of UCCRs to establish the diagnosis of hyperadrenocorticism and to identify PDH. The client is instructed to collect two urine samples from the dog on 2 consecutive mornings and store them in the refrigerator. After collection of the second urine sample, the client should administer 3 doses of dexamethasone (0.1 mg/kg/dose) to the dog orally at 8-hour intervals. Urine is collected on the morning of the third day, and all three

samples are delivered to the veterinarian for measurement of UCCRs. The first two urine samples are the screening test to diagnose hyperadrenocorticism. Abnormal values support hyperadrenocorticism; normal values rule out the disease. If both values are abnormal, then the average of the two values is used as the baseline value and compared with the third value obtained after dexamethasone administration. The dog is described as having responded to dexamethasone (suppressed) if the UCCR result from the third urine sample is less than 50% of the baseline value. Dogs meeting this criteria have results consistent with PDH, whereas those failing to demonstrate suppression could have either AT or PDH.

# Adrenocorticotropic Hormone Stimulation Test

The ACTH stimulation test is used to establish the diagnosis of hyperadrenocorticism and hypoadrenocorticism, identify iatrogenic hyperadrenocorticism, identify atypical hyperadrenocorticism (see p. 830), and monitor mitotane and trilostane treatment. ACTH stimulation test results do not distinguish between PDH and AT. In our experience ACTH stimulation test results are clearly abnormal in approximately 30%, in the borderline range in another 30% and within the reference range in approximately 40% of dogs with PDH. Identification of ACTH stimulation test results in the borderline range is common, and clearly abnormal test results occur in dogs that do not have hyperadrenocorticism. Because of problems with sensitivity and specificity combined with the high cost of ACTH, I do not routinely use the ACTH stimulation test when evaluating dogs for hyperadrenocorticism.

The protocol for the ACTH stimulation test is given in Table 53-2. When synthetic ACTH is being used, a lower dose (5 μg/kg, administered intravenously or intramuscularly) is also effective and the unused reconstituted ACTH can be stored frozen at -20°C in plastic syringes for 6 months with no adverse effects on bioactivity of the ACTH. Four ranges of values are used in the interpretation of the ACTH stimulation test (Fig. 53-14). Post-ACTH serum cortisol values between 6 and 18 | g/dl are within the normal reference range, values of 5 µg/dl and below are suggestive of iatrogenic hyperadrenocorticism or hypoadrenocorticism, values between 18 and 24 µg/dl are considered borderline for hyperadrenocorticism, and values greater than 24 µg/dl are supportive of hyperadrenocorticism, assuming the clinical findings and clinicopathologic data are consistent with the disease. An increased post-ACTH serum cortisol value, especially one between 18 and 24 µg/dl, does not by itself confirm a diagnosis of hyperadrenocorticism, especially if the clinical features and clinicopathologic data are not consistent with the diagnosis.

Post-ACTH serum cortisol concentrations that do not increase above the preadministration value suggest iatrogenic hyperadrenocorticism or spontaneous hypoadrenocorticism, especially if the cortisol values are below the normal baseline range (i.e., less than 5 µg/dl; see Fig. 53-14). A history of recent glucocorticoid administration and the

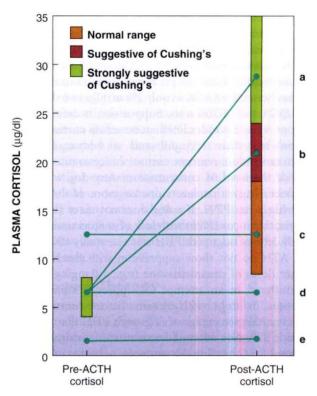


FIG 53-14

Interpretation of the adrenocorticotropic hormone (ACTH) stimulation test in dogs. Ideally, dogs with Cushing's syndrome have an increased post-ACTH administration cortisol concentration (line a). Post-ACTH cortisol values that fall into the "gray zone" (line b) could be consistent with Cushing's syndrome or result from the effects of concurrent illness or chronic stress. Post-ACTH cortisol values may also fall into the normal range in dogs with Cushing's syndrome. The absence of a response to ACTH stimulation is suggestive of adrenocortical neoplasia (lines c and d) or iatrogenic hyperadrenocorticism (lines d and e). History and physical examination findings should differentiate between these possibilities.

clinical presentation of the dog can help differentiate iatrogenic hyperadrenocorticism from spontaneous hypoadrenocorticism. In rare instances a dog with AT will have a minimal cortisol response to ACTH; however, its pre-ACTH and post-ACTH administration serum cortisol concentrations are within or above the reference range.

# High-Dose Dexamethasone Suppression Test

ATs function independently of pituitary ACTH; therefore, regardless of the dose, dexamethasone should never suppress the serum cortisol concentration if the source of the cortisol is an AT. In contrast, dexamethasone-induced suppression of ACTH secretion from a pituitary tumor is variable and may depend on the dexamethasone dose. The administration of increased amounts of dexamethasone should eventually suppress pituitary ACTH secretion in most dogs with PDH. The protocol for the high-dose dexamethasone suppression

(HDDS) test is similar to that for the LDDS test protocol, except that a higher dose (i.e., 0.1 mg/kg of body weight) of dexamethasone is used in an attempt to suppress pituitary ACTH secretion (see Table 53-2). Obtaining a 4-hour postdexamethasone blood sample is optional; in our experience, this has been informative in only 2% of dogs tested with both the LDDS and HDDS tests. Suppression is defined as a 4hour or 8-hour postdexamethasone serum cortisol concentration less than 1.5 µg/dl and a 4-hour or 8-hour postdexamethasone serum cortisol concentration less than 50% of the baseline concentration. Any dog with hyperadrenocorticism that meets one or more of these criteria most likely has PDH. If a dog does not meet any of these criteria, this is consistent with lack of suppression. Approximately 25% of dogs with PDH and essentially 100% of dogs with ATH do not show suppression with the HDDS test. Higher doses of dexamethasone (e.g., 1.0 mg/kg) could be administered in an attempt to suppress pituitary ACTH secretion in dogs with dexamethasone-resistant PDH. However, the percentage of dogs with PDH that show suppression at higher doses of dexamethasone is similar to that observed for the 0.1 mg/kg protocol.

# Endogenous Adrenocorticotropic Hormone Concentration

I do not routinely measure plasma ACTH concentrations because the LDDS test and abdominal ultrasound are very effective in differentiating between PDH and AT. I use plasma ACTH concentrations to provide clarity in confusing cases in which test results for hyperadrenocorticism and findings on abdominal ultrasound conflict (e.g., a dog with an adrenal mass but suppression on the LDDS test or a dog with an adrenal mass, enlargement of the contralateral adrenal gland, and lack of suppression on the LDDS test). Determination of a baseline plasma ACTH concentration is not used to diagnose hyperadrenocorticism because many of the concentrations in dogs with hyperadrenocorticism are within the reference range (2 to 25 pmol/L). However, determination of a single baseline plasma ACTH concentration may aid in distinguishing dogs with ATH from those with PDH once the diagnosis of hyperadrenocorticism is established. Adrenocortical tumors and iatrogenic hyperadrenocorticism should suppress ACTH secretion, and PDH is the result of excessive ACTH secretion (see Fig. 53-2). Approximately 60% of dogs with ATH have undetectable plasma ACTH concentrations, whereas 85% to 90% of dogs with PDH have plasma ACTH concentrations greater than 10 pmol/L and 35% have ACTH concentrations greater than 25 pmol/L. Plasma ACTH concentrations of 2 to 10 pmol/L are nondiagnostic. Several commercial veterinary endocrine laboratories perform endogenous ACTH assays for dogs. The laboratory should be consulted for information on sample collection and handling; results should be interpreted on the basis of the reference range established for the laboratory being used.

#### **Medical Treatment**

Medical options for treating hyperadrenocorticism are listed in Table 53-3. The most viable treatment options for dogs are mitotane and trilostane.

# **MITOTANE**

Chemotherapy using mitotane (0,0'DDD; Lysodren; Bristol Myers Oncology) is the most commonly used treatment for PDH and is a viable alternative to adrenalectomy for treatment of ATs causing hyperadrenocorticisim. There are two treatment protocols: the traditional approach, the goal of which is to control the hyperadrenal state without causing clinical signs of hypoadrenocorticism, and medical adrenalectomy, the goal of which is to destroy the adrenal cortex and create hypoadrenocorticism. I prefer the traditional approach initially and consider medical adrenalectomy in dogs that fail to respond to the traditional approach or that become non-responsive to mitotane after months or years of maintenance therapy.

# Traditional Approach to Mitotane Treatment

For the traditional approach, there are two phases of mitotane therapy: an initial induction phase designed to gain control of the disorder, and a lifelong maintenance phase designed to prevent recurrence of the signs of the disease.



TABLE 53-3

Drugs that Have Been Used to Treat Hyperadrenocorticism in Dogs

DRUG	MECHANISM OF ACTION	INDICATIONS	INITIAL DOSAGE	EFFICACY
Mitotane	Lysis of adrenal cortex	PDH, ATH	50 mg/kg divided q12h with food	>80%
Trilostane	Inhibition of cortisol biosynthesis	PDH, ATH	0.5 to 1.0 mg/kg q12h	~80%
Ketoconazole	Inhibition of cortisol biosynthesis	PDH, ATH	5 mg/kg q12h	<75%
Deprenyl	Inhibition of dopamine metabolism*	PDH	1 mg/kg q24h	<20%
Cyproheptadine	Serotonin antagonist†	PDH	_	<10%
Bromocriptine	Dopamine agonist	PDH	<del></del>	<10%

PDH, Pituitary-dependent hyperadrenocorticism; ATH, adrenal tumor causing hyperadrenocorticism.

<sup>\*</sup>CNS dopamine suppresses CRH and ACTH secretion.

<sup>†</sup> CNS serotonin stimulates CRH and ACTH secretion.

# **Induction Therapy**

The mitotane dosage during induction therapy is 40 to 50 mg/kg, divided into two doses. The daily dosage is reduced to 25 to 35 mg/kg in dogs without polydipsia or with concurrent diabetes mellitus. Gastrointestinal absorption of mitotane is enhanced in the presence of fat. Mitotane is more effective when each dose is ground up, mixed with a small amount of vegetable oil, and administered with food. Concurrent prednisone administration (0.25 mg/kg q24h) during induction therapy is a matter of personal preference. If prednisone is not used during induction therapy, it should always be dispensed before beginning induction therapy so that the client has glucocorticoids on hand should adverse reactions to mitotane develop.

The induction phase of mitotane treatment is typically done with the dog in the home environment. Client awareness of their dog's activity, mental awareness, appetite, water consumption, and overall well-being is imperative for success. The usual amount of food offered to the dog can be decreased by approximately 25% during the induction phase to ensure that the dog remains hungry. Clients are instructed to stop mitotane treatment and contact their veterinarian if they observe lethargy, inappetence, vomiting, weakness, decreased water intake, or any other change in their dog that does not seem right. The veterinarian or a technician should call the client every day, beginning with the second day of therapy, to check on the health of the dog. The induction phase of therapy is usually complete once any reduction in appetite is noted or once daily water consumption decreases into the normal range (i.e., 80 ml/kg or less). Control is confirmed with the ACTH stimulation test. The first ACTH stimulation test should be performed 5 to 7 days after starting induction therapy, even if clinical signs of hyperadrenocorticism persist. Dogs that have responded clinically to the medication (or if the client is not certain about response) should not receive further therapy until results of the ACTH stimulation test are known. Dogs that have not yet responded clinically should undergo an ACTH stimulation test but should also remain on daily mitotane therapy pending results of the ACTH stimulation test.

The goal of therapy is to achieve a post-ACTH serum cortisol concentration of 2 to 5  $\mu$ g/dl. Daily mitotane therapy and weekly ACTH stimulation tests should be continued until a post-ACTH serum cortisol concentration falls within the desired range or signs of hypocortisolism develop. In most dogs clinical signs resolve and a post-ACTH serum cortisol concentration of less than 5  $\mu$ g/dl is achieved within 5 to 10 days of the start of the daily administration of 40 to 50 mg of mitotane/kg. A small number of dogs respond in less than 5 days, and an equally small number of dogs show minimal improvement after 20 to 30 consecutive days of therapy

Reasons for a prolonged or poor response to mitotane treatment include inadequate dose, inadequate absorption from the gastrointestinal tract, concurrent administration of drugs (e.g., phenobarbital) that stimulate hepatic microsomal drug-metabolizing enzymes and could accelerate the

metabolism of mitotane and decrease its serum concentration, existence of an AT rather than PDH, and client compliance issues. The absorption of mitotane is improved if it is given with food, especially a fatty meal, and if the tablet is crushed, mixed with a small amount of vegetable oil, and mixed with food. Typically, dogs with AT are more resistant to the adrenocorticolytic effects of mitotane than dogs with PDH. If tests to differentiate PDH from AT were not performed, dogs that are shown to be resistant to therapy, defined as showing little or no reduction in the post-ACTH plasma cortisol concentration after 20 or more days of therapy, should undergo further evaluation (i.e., abdominal ultrasound) to determine whether an AT is an explanation for the resistance. Rarely, dogs with PDH require more than 30 consecutive days of mitotane therapy before the desired response is seen.

# **Maintenance Therapy**

Mitotane must be administered periodically to prevent recurrence of clinical signs. The maintenance phase of mitotane therapy should be initiated once the post-ACTH serum cortisol concentration is less than 5 µg/dl and the dog appears healthy. The maintenance dose is defined as the weekly amount of mitotane administered, regardless of whether the weekly dose is given once per week or divided into multiple doses and given on several days. Adverse reactions caused by sensitivity to the drug are less likely to occur when the weekly dose is divided and given on several days of the week. The typical initial weekly maintenance dosage of mitotane is 50 mg/kg administered orally, divided into two or three doses, and administered on 2 or 3 days of each week (e.g., Monday and Thursday or Monday, Wednesday, and Friday). The maintenance dose of mitotane is decreased from 50 mg/ kg/week to 25 mg/kg/week if the post-ACTH serum cortisol concentration is less than 2 µg/dl and the dog appears healthy. Mitotane treatment is discontinued and prednisone treatment initiated if the post-ACTH serum cortisol concentration is less than 2 µg/dl and the dog is exhibiting clinical signs of hypoadrenocorticism (i.e., lethargy, inappetence, vomiting).

The initial dose of lysodren during maintenance therapy is arbitrary, and subsequent adjustments are made on the basis of results of ACTH stimulation tests; the first test is performed 3 to 4 weeks after the start of maintenance therapy. The goal of maintenance therapy is to maintain the post-ACTH serum cortisol concentration between 2 and 5 µg/dl in an otherwise healthy dog. The dose and frequency of administration of mitotane are adjusted, as needed, to maintain a hypoadrenal response to ACTH administration. If the post-ACTH serum cortisol is between 2 and 5 µg/dl, a change in treatment is not indicated and the ACTH stimulation test should be repeated in 6 to 8 weeks. If the post-ACTH serum cortisol concentration is greater than 5 µg/dl, the amount of mitotane per administration or the frequency of administration is increased; if the post-ACTH serum cortisol concentration is less than 2 µg/dl, the mitotane dose or frequency of administration is decreased; mitotane therapy is temporarily discontinued if clinical signs of hypoadrenocorticism are present. An ACTH stimulation test is performed 3 to 4 weeks after changing the dose or frequency of administration of mitotane. Once the post-ACTH serum cortisol concentration is stable and in the range of 2 to 5 µg/dl, the ACTH stimulation test should be repeated every 3 to 6 months thereafter unless clinical signs of hyperadrenocorticism or hypoadrenocorticism develop. In most dogs an initially effective maintenance dose of mitotane becomes inadequate as the compensatory sustained increase in plasma ACTH concentration counters the adrenocorticolytic effects of mitotane. With time (i.e., months to years), the dose and frequency of administration of mitotane must usually be increased to compensate for this effect. Periodic ACTH stimulation testing will identify an increase in the post-ACTH serum cortisol concentration above 5 µg/dl, allowing the clinician to adjust the mitotane treatment protocol before clinical signs of hyperadrenocorticism develop and another round of induction therapy is needed. In some dogs this can ultimately necessitate daily mitotane administration, sometimes with poor control of the disorder. Alternative therapy (i.e., medical adrenalectomy using mitotane, trilostane) should be considered for dogs that become insensitive to mitotane

#### **Adverse Reactions to Mitotane Treatment**

Adverse reactions to mitotane treatment result from sensitivity to the drug or from excessive administration and the subsequent development of glucocorticoid and, if severe, mineralocorticoid deficiency (Box 53-4). The most common reactions to mitotane are gastric irritation and vomiting occurring shortly after its administration. If the gastric upset is the result of drug sensitivity and not hypoadrenocorticism, dividing the dose further, increasing the interval between administrations, or both can help minimize vomiting.

The excessive administration of mitotane results in clinical signs of hypocortisolism, including weakness, lethargy, anorexia, vomiting, and diarrhea. Clinical improvement is usually seen within hours of the administration of prednisone (0.25 to 0.5 mg/kg, administered orally). If the dog responds, the initial dosage of glucocorticoids should be continued for 3 to 5 days and then gradually decreased and stopped over the ensuing 1 to 2 weeks. Mitotane therapy should be stopped until the dog is normal when it is not receiving glucocorticoids. An ACTH stimulation test performed once the dog is healthy and not receiving glucocorticoids can help determine when to start mitotane treatment. Ideally, mitotane treatment should be started when the post-ACTH serum cortisol concentration is  $2 \mu g/dl$  or greater. The weekly dose of mitotane should be reduced when therapy is reinitiated.

Excessive administration of mitotane ultimately causes hypoaldosteronism. Mineralocorticoid deficiency should be considered in any dog with signs of hypocortisolism that does not respond to glucocorticoid therapy. Finding hyponatremia and hyperkalemia supports a diagnosis of hypoaldosteronism, and mineralocorticoid therapy is indicated in such dogs (see p. 840). Hypoaldosteronism can develop within



BOX 53-4

Adverse Effects of Mitotane in Dogs

#### Direct Effect\*

Lethargy

Inappetence

Vomiting

Neurologic signs

Ataxia

Circling

Stupor

Apparent blindness

#### Secondary to Overdosage\*

Hypocortisolism

Lethargy

Anorexia

Vomiting

Diarrhea Weakness

Hypoaldosteronism (hyperkalemia, hyponatremia)

. Lethargy

Weakness

Cardiac conduction disturbances

Hypovolemia

Hypotension

PMA, Pituitary macroadenoma.

\* Adrenocorticotropic hormone stimulation test, serum electrolytes, response to discontinuation of mitotane, and response to glucocorticoid therapy are used to differentiate these categories of adverse reactions.

days of the start of mitotane therapy in some dogs. Hypoal-dosteronism can resolve and hyperadrenocorticism recur spontaneously, but this is unpredictable. Some dogs remain mineralocorticoid deficient for the remainder of their lives.

Mitotane may induce the development of neurologic signs, including stupor, head pressing, pacing, circling, seizures, ataxia, and blindness. Neurologic signs are usually transient, typically last 24 to 48 hours after mitotane administration, and usually occur in dogs that have been receiving the drug for more than 6 months. The primary differential diagnoses in such animals are pituitary macrotumor syndrome (see p. 814), hypoadrenocorticism, and thromboemboli. Adjustments in the dose or frequency of mitotane administration or temporary discontinuation of the therapy may alleviate the neurologic signs. An alternative mode of therapy should be considered if neurologic signs persist (discussed in more detail later).

# Management of Concurrent Diabetes Mellitus

Hyperadrenocorticism and diabetes mellitus are common concurrent diseases in dogs. Presumably, hyperadrenocorticism develops initially and subclinical diabetes mellitus becomes clinically apparent as a result of the insulin resistance caused by the hyperadrenal state. For most of these

dogs, glycemic control remains poor despite insulin therapy, and good glycemic control is generally not possible until the hyperadrenocorticism is controlled. Occasionally, diabetic dogs presumably in the early stages of hyperadrenocorticism (often identified while pursuing the cause for an increased ALP) will be responsive to insulin and have good control of glycemia. Because the diabetes is well controlled, the decision to treat or not treat the hyperadrenocorticism in these dogs should be based on other factors, such as the presence of additional clinical signs or physical examination findings and the clinician's index of suspicion for the disease. The clinician should adopt a wait-and-see approach in the absence of strong evidence for hyperadrenocorticism in these dogs. Poor control of the diabetic state will eventually occur if hyperadrenocorticism is present.

The initial focus should be on treating the hyperadrenal state in a poorly controlled diabetic dog diagnosed with hyperadrenocorticism. Insulin therapy is indicated during induction therapy; however, aggressive efforts to control the blood glucose concentration should not be attempted. Rather, a conservative dose (0.5 to 1.0 U/kg) of intermediate-acting insulin (i.e., lente or NPH) is administered twice a day to prevent ketoacidosis and severe hyperglycemia (blood glucose concentration greater than 500 mg/dl). Monitoring induction therapy in the hyperadrenal dog with concurrent diabetes mellitus is similar to that used for the hyperadrenal dog (see the section on monitoring induction therapy) with one exception. Monitoring water consumption is not reliable when concurrent diabetes mellitus is present because both diseases cause polyuria and polydipsia and because polyuria and polydipsia may persist if poor control of glycemia persists despite the fact that the hyperadrenocorticism is under control. As control of the hyperadrenocorticism is achieved, insulin antagonism caused by the hyperadrenocorticism resolves and tissue sensitivity to insulin improves. To help prevent hypoglycemic reactions, clients are asked to test urine for the presence of glucose, preferably two or three times each day. Any urine sample found to be negative for glucose should be followed by a 20% to 25% reduction in the insulin dose and performance of an ACTH stimulation test. Critical assessment of glycemic control and adjustments in insulin therapy, if indicated, should be initiated once hyperadrenocorticism is controlled and maintenance mitotane therapy initiated.

## Medical Adrenalectomy Using Mitotane

An alternative to the traditional mitotane treatment protocol is to intentionally cause complete destruction of the adrenal cortices by administering an excessive amount of mitotane. In theory, therapy for the ensuing adrenocortical insufficiency would then be necessary for the life of the dog. The protocol consists of administering mitotane at a dosage of 75 to 100 mg/kg daily for 25 consecutive days, given in three or four doses per day, with food, to minimize neurologic complications and ensure good intestinal absorption of the drug. Lifelong prednisone (0.1 to 0.5 mg/kg q12h initially) and mineralocorticoid (see p. 840) therapy is begun at the start of

mitotane administration. The prednisone dose is tapered after completion of the 25-day protocol. Unfortunately, relapse with signs of hyperadrenocorticism occurs within the first year alone in approximately 33% of dogs so treated, indicating the need for periodic ACTH stimulation testing similar to that done in animals treated with the traditional mode of therapy. In addition, this treatment can be considerably more expensive than long-term treatment with mitotane because of the expense of treating addisonian dogs. For these reasons, medical adrenalectomy is reserved for dogs that show a poor response to the traditional form of treatment.

#### **TRILOSTANE**

Trilostane (Vetoryl, Arnolds Veterinary Products) is a competitive inhibitor of 3-β-hydroxysteroid dehydrogenase, which mediates the conversion of pregnenolone to progesterone in the adrenal gland. The net effect is inhibition of cortisol production (Fig. 53-15). Trilostane is currently the preferred enzyme blocker for treating hyperadrenocorticism. The clinical efficacy of trilostane is excellent (approximately 80%), and trilostane can control clinical signs of hyperadrenocorticism in dogs for prolonged periods of time (longer than 1 year). Trilostane is used as the primary treatment modality for PDH in dogs, as an alternative in dogs in which mitotane is ineffective or not usable because of problems with drug sensitivity, and as a way to reverse the metabolic derangements of hyperadrenocorticism before adrenalectomy. Trilostane is currently available as 30-, 60-, and 120mg capsules. Compounding of capsules to different strengths (e.g., 10 or 20 mg) may be required. The published initial treatment protocol is 30 mg once a day for dogs weighing less than 5 kg, 60 mg once a day for dogs weighing 5 to 20 kg, 120 mg once a day for dogs weighing 20 to 40 kg, and 180 mg once a day for dogs weighing more than 40 kg. However, in our experience, twice-daily dosing using a lower dose provides better control than once-daily dosing using the aforementioned dosing schedule and the occurrence and severity of adverse reactions are less frequent. Our approach is to begin treatment using a trilostane dosage between 0.5 and 1 mg/kg twice daily.

The dosage and frequency of administration of trilostane are adjusted, as needed, until clinical signs are controlled. An ACTH stimulation test and serum electrolytes should be performed 10 to 14 days after initiation of treatment and 4 to 6 hours after trilostane administration. In addition, the client should bring in a urine sample collected at home the morning of the ACTH stimulation test for a UCCR. The goals of therapy are the same as those of mitotane therapy: clinical improvement without the development of illness, lack of an adrenocortical response to ACTH, and a normal UCCR. Results of the ACTH stimulation test are used to adjust the dosage of trilostane; the goal is a post-ACTH cortisol concentration between 2 and 5 µg/dl. The UCCR is used to determine frequency of trilostane administration in dogs receiving the drug once daily. If clinical signs persist, results of the ACTH stimulation test are indicative of control of the disease, and the UCCR is increased, then the frequency

#### FIG 53-15

Steroid biosynthetic pathways in the adrenal cortex. The branching pathways for glucocorticoids, mineralocorticoids, and adrenal androgens are shown. The site of blockade in the steroid biosynthetic pathways by the enzyme inhibitors trilostane (T), ketoconazole (K), metyrapone (M), and aminoglutethimide (A) are also shown.

of trilostane administration should be increased to twice a day. Serum electrolytes are monitored for changes consistent with the onset of hypoaldosteronism. Once control of the hyperadrenal state is attained, an ACTH stimulation test, serum electrolytes, and UCCR should be evaluated every 3 to 4 months.

Adverse effects of trilostane include lethargy, vomiting, and electrolyte shifts compatible with hypoadrenocorticism. Permanent hypoadrenocorticism has been reported in a small number of dogs. Histopathologic examination of the adrenal gland in dogs treated with trilostane has revealed adrenocortical necrosis of variable severity in some dogs—findings that, if severe, could explain persistent hypoadrenocorticism in affected dogs. Acute death has been reported in a small number of dogs shortly after the initiation of trilostane treatment.

#### KETOCONAZOLE

Ketoconazole reversibly inhibits adrenal steroidogenesis (see Fig. 53-15). The initial dosage of ketoconazole is 5 mg/kg q12h, and subsequent increases in the dosage are based on results of an ACTH stimulation test performed 10 to 14 days later and while the dog is still receiving ketoconazole. The goals of therapy are similar to those discussed for trilostane. Approximately 20% to 25% of dogs do not respond to the drug as a result of poor intestinal absorption. Adverse reactions are primarily a result of hypocortisolism and include lethargy, inappetence, vomiting, and diarrhea. Unfortunately, it is difficult to control the clinical signs of hyperadrenocorticism without creating problems with hypocortisolism.

## L-DEPRENYL

L-Deprenyl (Anipryl, Deprenyl Animal Health) inhibits dopamine metabolism and increases hypothalamic and pituitary concentrations of dopamine, which in turn inhibits corticotropin-releasing hormone (CRH) and ACTH secretion. The current dosage recommendation for L-Deprenyl is 1 mg/kg once daily initially, with an increase to 2 mg/kg once daily if there is no response after 2 months. The efficacy of

this drug for the treatment of PDH is, at best, 20%. The vast majority of dogs with PDH have a pituitary tumor, not alterations in neurotransmitter control of hypothalamic-pituitary gland function. Concentrations of an endogenous amphetamine, phenylethylamine, increase in the brains of dogs treated with L-Deprenyl, which may improve the dog's level of activity and its interactions with family members independent of any improvement in the hyperadrenal state.

## **ADRENALECTOMY**

Adrenalectomy is the treatment of choice for an AT unless metastatic lesions or invasion of surrounding organs or blood vessels is identified during the preoperative evaluation; the dog is considered a poor anesthetic risk because it has a concurrent disease (e.g., heart failure) or is debilitated as a result of its hyperadrenal state; or the probability of perioperative thromboembolism is considered high because of systemic hypertension, an increased urine protein: creatinine ratio, or a decreased serum antithrombin III concentration. The probability of successful adrenalectomy is lower and the likelihood of perioperative complications is greater the larger the adrenal mass. Removal of an adrenal mass that has a diameter in excess of 6 cm can be difficult even when the surgery is performed by an experienced surgeon. The larger the adrenal mass, the greater the probability that the adrenal mass is a carcinoma and that metastasis has occurred, regardless of findings during the preoperative evaluation. Treatment with mitotane or trilostane offers a viable alternative to adrenalectomy, especially for aged dogs or dogs at increased risk for anesthetic, surgical, or postsurgical problems. (See Suggested Readings for detailed information on surgical techniques.)

The most worrisome complication of adrenalectomy is thromboembolism, which typically develops during or within 72 hours of surgery and carries a high mortality rate (see p. 814). Several steps help minimize this complication. Trilostane treatment for 3 to 4 weeks before surgery can reverse the metabolic derangements of hyperadrenocorticism and minimize many of the complications associated with adrenalectomy. Plasma is a source of antithrombin III and should be administered during surgery. Heparin or other anticoagulant therapy should be administered during and for several days after adrenalectomy (see Chapter 12). Dogs should go for frequent short walks within hours of the surgery to promote blood flow and minimize clot formation. Anesthetic drugs and pain medications should be administered at dosages that allow the dog to be ambulatory within 4 hours of the surgery. Despite these measures, thromboembolism remains a common perioperative complication that should be thoroughly discussed with clients who are considering adrenalectomy.

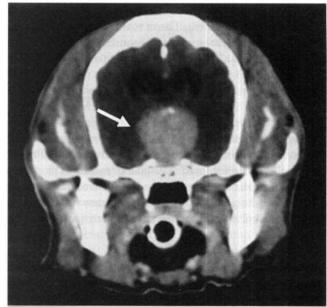
Glucocorticoid therapy is not indicated before adrenalectomy because it may worsen hypertension, cause overhydration, and increase the risk of thromboembolic episodes. Beginning with anesthesia, IV fluids should be administered at a surgical maintenance rate. Acute hypocortisolism uniformly occurs after adrenalectomy. After the surgeon identi-

fies the adrenal tumor, dexamethasone (0.05 to 0.1 mg/kg) should be placed in the IV infusion bottle. This dose should be given over a 6-hour period. A tapering dose (e.g., decreasing the dose by 0.02 mg/kg/24 h) of dexamethasone should continue to be administered intravenously at 12-hour intervals until the dog can safely be given oral medication without the danger of vomiting (typically 24 to 72 hours postoperatively). At that point, the glucocorticoid supplement should be switched to oral prednisone (0.25 to 0.5 mg/kg q12h). Once the dog is eating and drinking on its own, the frequency of prednisone administration should be decreased to once a day and given in the morning. The prednisone dosage is then gradually reduced during the ensuing 3 to 4 months. If a unilateral adrenalectomy has been performed, prednisone supplementation can eventually be discontinued once the contralateral normal adrenocortical tissue becomes functional. Lifelong prednisone at a dosage of 0.1 to 0.2 mg/ kg administered once or twice daily is usually required for dogs that undergo bilateral adrenalectomy.

Serum electrolyte concentrations should be closely monitored postoperatively. Development of mild hyponatremia and hyperkalemia is common within 72 hours of surgery and usually resolves in a day or two as exogenous glucocorticoid doses are reduced and the dog begins to eat. Mineralocortioid treatment is recommended if the serum sodium concentration decreases to less than 135 mEq/L or serum potassium concentration increases to greater than 6.5 mEq/ L. An injection of desoxycorticosterone pivalate (DOCP; Percorten-V; Novartis Pharmaceuticals) is recommended, with measurement of serum electrolytes performed 25 days after the injection (see p. 840). If the dog is healthy and serum electrolytes are normal on day 25, the dog should be reevaluated 7 days later. If serum electrolytes are still normal, additional DOCP treatment is not needed. If hyponatremia or hyperkalemia is identified on day 25, another injection of DOCP should be administered but with the dosage reduced by 50% and serum electrolytes evaluated 25 days later.

#### RADIATION THERAPY

Approximately 50% of dogs have a pituitary mass identified on CT or MRI at the time PDH is diagnosed. In approximately 50% of these dogs, the pituitary mass grows over the ensuing 1 to 2 years, eventually causing pituitary macrotumor syndrome (see p. 814). Pituitary macroadenoma is tentatively diagnosed by ruling out other causes of the neurologic disturbances and is confirmed by CT or MRI findings (see Fig. 53-4). Development of neurologic signs from a pituitary macrotumor is a common reason for clients to request euthanasia of dogs with PDH. Irradiation has successfully reduced the tumor size and lessened or eliminated neurologic signs in dogs with pituitary macrotumor syndrome (Fig. 53-16). The primary mode of radiation treatment is cobalt 60 photon irradiation or linear accelerator photon irradiation. Treatment usually involves the delivery of a predetermined total dose of radiation given in fractions over a period of several weeks. Currently a total dose of 48 Gy, given in 4 Gy doses 3 to 5 days per week for 3 to 4 weeks, is typi-



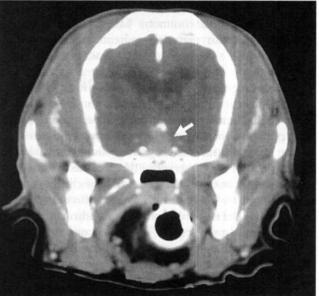


FIG 53-16

**A**, Computed tomography (CT) image of the pituitary region of a 9-year-old, female spayed Cocker Spaniel with pituitary-dependent hyperadrenocorticism (PDH). The PDH had been treated with mitotane for 2 years, at which time the dog developed lethargy, inappetence, and weight loss. A large mass measuring approximately 2.0 cm in diameter is evident in the hypothalamic-pituitary region (arrow). **B**, CT image of the pituitary region 18 months after completion of radiation therapy. The volume of the mass decreased by approximately 75%, compared with the volume before treatment. Clinical signs related to the pituitary macrotumor resolved, and mitotane treatment was discontinued after radiation treatment.

cally administered to hyperadrenal dogs with pituitary macroadenoma at our hospital.

Prognostic factors that affect survival time after radiation therapy include the severity of neurologic signs and the relative size of the tumor. Generally, dogs with subtle or mild В

neurologic clinical signs and the smallest tumors show the best response to treatment. Theon et al. (1998) found a mean survival time after radiation of 25 months in dogs with mild neurologic signs, 17 months in dogs with severe neurologic signs, and only 5 months in untreated dogs with neurologic signs. Because of the high prevalence of a pituitary mass at the time PDH is diagnosed and the potential for future growth and development of neurologic signs, examination of the pituitary gland using CT or MRI and radiation therapy if a mass is identified should be discussed with the client at the time PDH is diagnosed. The goal of radiation therapy is to shrink the mass and prevent development of macrotumor syndrome; mitotane or trilostane therapy may still be needed to control clinical signs of hyperadrenocorticism.

# **Prognosis**

The average life expectancy in dogs with adrenal-dependent hyperadrenocorticism that survive the initial postadrenalectomy month is approximately 36 months. Dogs with adrenocortical adenoma and adrenocortical carcinoma that has not metastasized (uncommon) have a good prognosis, whereas dogs with metastatic adrenocortical carcinoma (common) have a poor prognosis, with these dogs typically succumbing to the disease within a year of diagnosis. Although clinical signs can be controlled with trilostane and mitotane, death ultimately results from the debilitating effects of the tumor, complications of hyperadrenocorticism (e.g., pulmonary thromboembolism), or other geriatric disorders (e.g., renal insufficiency, congestive heart failure).

The prognosis for dogs with PDH depends in part on the age and overall health of the dog and on the client's commitment to therapy. The mean life span of affected dogs after diagnosis of PDH is approximately 30 months. Younger dogs may live considerably longer (i.e., 5 years or longer). Many dogs ultimately die or are euthanized because of complications related to hyperadrenocorticism (e.g., pituitary macrotumor syndrome) or other geriatric disorders.

# ATYPICAL CUSHING'S SYNDROME IN DOGS

Dogs with atypical Cushing's syndrome have clinical features suggestive of hyperadrenocorticism but persistently normal or equivocal endocrine test results. An imbalance of one or more of the adrenocortical steroid hormone intermediates required for synthesis of cortisol (see Fig. 53-15) is believed to be the cause. It has been hypothesized that a relative deficiency in enzymes required for cortisol synthesis (such as 21- $\beta$ -hydroxylase or 11- $\beta$ -hydroxylase) cause accumulation of steroid precursors proximal to the blockade in the synthetic pathway. High concentrations of one or more steroid precursors may cause clinical signs or may be shunted into alternative metabolic pathways and cause excesses in other steroid hormones, such as androstenedione. Increased serum adrenocortical steroid hormone intermediates often occur in conjunction with cortisol in dogs with PDH and cortisol-

secreting ATs. In contrast, dogs with atypical Cushing's syndrome have normal or inconclusive serum cortisol concentrations and an increase in one or more adrenocortical steroid hormone intermediates, most notably 17-hydroxy-progesterone.

Adrenal tumors that secrete progesterone and 17-hydroxyprogesterone cause a clinical syndrome that mimics hyperadrenocorticism in dogs and cats. Clinical signs presumably result from intrinsic glucocorticoid activity of progestins, progestin-induced displacement of cortisol from cortisolbinding protein in the circulation, or both. An atypical form of PDH has also been described in which clinical features mimic hyperadrenocorticism, abdominal ultrasound reveals adrenal glands that are normal or mildly increased in size, tests of the pituitary-adrenocortical axis are normal or inconclusive, pre- and post-ACTH serum 17-hydroxyprogesterone concentrations are increased, and clinical signs improve with mitotane treatment. Diagnosis requires evaluation of serum and plasma adrenocortical steroid hormone intermediates and sex hormones before and 1 hour after the IV administration of 5 μg/kg of synthetic ACTH (Cosyntropin). The most common abnormality is an increase in serum 17-hydroxyprogesterone concentration. Currently, the only laboratory with established normal values for precursor and sex steroids is the Endocrinology Laboratory at the University of Tennessee, College of Veterinary Medicine, Knoxville, TN 37901-1071. Treatment recommendations have included low dosages of mitotane (10 mg/kg/day initially) and trilostane, although Sieber-Ruckstuhl et al. (2006) failed to document a decrease in 17-hydroxyprogesterone concentrations in dogs with PDH treated with trilostane.

I do not routinely measure serum adrenocortical steroid hormone intermediates or sex hormones when initially evaluating dogs for hyperadrenocorticism. I reserve measurement of these hormones for those dogs with clinical features suggestive of hyperadrenocorticism but persistently normal or equivocal test results for hyperadrenocorticism.

## HYPERADRENOCORTICISM IN CATS

Hyperadrenocorticism is uncommon in cats. Although many of the clinical characteristics of feline hyperadrenocorticism are similar to those seen in dogs, there are some important differences that should be emphasized. Most notable is the very strong association with diabetes mellitus; the progressive, relentless weight loss leading to cachexia; and dermal and epidermal atrophy leading to extremely fragile, thin, easily torn and ulcerated skin (i.e., feline fragile skin syndrome) in cats with hyperadrenocorticism. Establishing the diagnosis can be difficult, and effective medical treatment for hyperadrenocorticism in cats has yet to be identified.

# Etiology

Hyperadrenocorticism in cats is classified as either pituitary dependent (PDH) or adrenocortical tumor dependent (ATH). Approximately 80% of cats with hyperadrenocorti-

cism have PDH and 20% have ATH, with 50% of ATHs being adenomas and 50% carcinomas. Cats with PDH have a pituitary microadenoma, macroadenoma, or carcinoma identified at necropsy. Iatrogenic hyperadrenocorticism is uncommon in cats and typically takes months of prednisone or prednisolone administration before clinical signs occur.

#### **Clinical Features**

# CLINICAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Hyperadrenocorticism is a disease of older (average age 10 years) mixed-breed cats. There is a strong correlation between hyperadrenocorticism and diabetes mellitus, and the most common initial clinical signs of feline hyperadrenocorticism (i.e., polyuria, polydipsia, polyphagia) are more likely caused by diabetes than by hyperadrenocorticism. Other clinical signs and physical examination findings are not as frequently observed in cats as in dogs and tend to be very subtle in the early stages of the disease (Box 53-5; Fig. 53-17).

A frequent clue to the existence of hyperadrenocorticism in cats is the presence of diabetes mellitus that is difficult to control and ultimately progresses to severe insulin resistance. Initially, clinical signs of hyperadrenocorticism are mild and tests of the pituitary-adrenocortical axis are often inconclusive and difficult to interpret in the presence of poorly controlled diabetes. With time, hyperadrenocorticism becomes more apparent as affected cats become progressively more debilitated despite aggressive insulin therapy; weight loss leads to cachexia; and dermal and epidermal atrophy result in extremely fragile, thin, easily torn, and ulcerated skin (Fig. 53-18). Dermal and epidermal lesions often occur when the cat is groomed or when the cat is handled during the physical examination. Insulin resistance is usually quite severe by

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BOX 53-5

Clinical Features of Hyperadrenocorticism in Cats

## Clinical Signs

Polyuria, polydipsia\* Polyphagia\* Patchy alopecia\* Unkempt haircoat\*

Symmetric alopecia

Lethargy

Thin, easily torn skin (feline fragile skin syndrome)\*
Weight loss\*

Drooping of pinna

# Additional Physical Findings

"Pot-bellied" appearance\*
Hepatomegaly\*
Muscle wasting\*
Skin infections

the time cachexia and skin fragility develop. The primary differential diagnosis for insulin resistance, cachexia, and feline fragile skin syndrome is excess progestins such as that which occurs with progesterone-secreting adrenal tumors (see p. 844).

# **CLINICAL PATHOLOGY**

The classic clinicopathologic alterations seen in dogs with hyperadrenocorticism are infrequently found in cats. The most frequently observed abnormalities in cats are hyperglycemia, glycosuria, hypercholesterolemia, and a mild increase in alanine aminotransferase activity. These alterations can be explained by concurrent, poorly regulated diabetes mellitus. A stress leukogram, an increase in ALP activity, and isosthenuric-hyposthenuric urine are not common findings in hyperadrenal cats. An inability to document histologic changes in the liver consistent with steroid-induced hepatopathy, an absence of the steroid-induced alkaline phosphatase isoenzyme activity, and the relatively short half-life of ALP activity in cats may account for the absence of an observed increase in ALP activity. Urine abnormalities frequently identified in dogs with hyperadrenocorticism are not common in cats.

#### DIAGNOSTIC IMAGING

Abdominal ultrasonography is used to identify adrenal masses and to clarify the clinician's index of suspicion for PDH. The interpretation of results of adrenal imaging in cats is similar to that in dogs (see p. 815). The maximum width of the adrenal gland in healthy cats is typically less than 0.5 cm. Adrenomegaly should be suspected when the maximum width is greater than 0.5 cm; a maximum width greater than 0.8 cm is strongly suggestive of adrenomegaly. The finding of easily visualized, bilaterally large adrenals in a cat with appropriate clinical signs, physical examination findings, and abnormal test results of the pituitary-adrenocortical axis is strong evidence for PDH. CT and MRI can be used to look for pituitary macroadenoma and to assess the size of an adrenal mass and extent of infiltration of the mass into surrounding blood vessels and organs before adrenalectomy.

# TESTS OF THE PITUITARY-ADRENOCORTICAL AXIS

Although the tests used to diagnose hyperadrenocorticism in cats and dogs are similar (see p. 818), there are some important differences in the testing protocol and in the interpretation of results (Table 53-4). I rely most heavily on the UCCR, dexamethasone suppression test, and abdominal ultrasonography to establish the diagnosis of hyperadrenocorticism in cats. The ACTH stimulation test lacks sensitivity in the cat and is not recommended. I also rely on abdominal ultrasound rather than endogenous plasma ACTH concentration to differentiate PDH from ATH.

#### **Urine Cortisal/Creatinine Ratio**

The theory behind and the specifics regarding the UCCR are similar for dogs and cats and discussed on p. 819. The cat

<sup>\*</sup> Common.



A and B, A 9-year-old cat with pituitary-dependent hyperadrenocorticism (PDH) and insulin-resistant diabetes mellitus. Note the relatively normal physical appearance of the cat in its normal posture (A). Abdominal enlargement and inguinal alopecia are evident on physical examination (B). C and D, A 16-year-old cat with PDH and insulin-resistant diabetes mellitus. Note the relatively normal appearance of the cat and the alopecia and ulceration in the dorsal cervical and anterior thoracic region in the area of a collar worn by the cat. Alopecia was also present in the ventral region of the neck.

reference range for the UCCR performed on urine collected at home is less than  $3.6 \times 10^{-5}$  (often listed as less than 36); this value may vary among laboratories. I use the UCCR as the initial screening test for hyperadrenocorticism in cats. A normal UCCR is a strong finding against the diagnosis; an increased ratio does not establish the diagnosis by itself but supports performing the dexamethasone suppression test.

## **Dexamethasone Suppression Test**

The duration of the suppressive effects of intravenously administered dexamethasone on serum cortisol concentrations is more variable in cats than dogs. Approximately 20% of healthy cats do not experience the suppressive effects of dexamethasone, and their serum cortisol concentrations are greater than 1.4 ug/dl 8 hours after dexamethasone administration. This "escape phenomenon" is more likely to occur in cats receiving lower doses of dexamethasone. Because of potential misinterpretation caused by the escape phenome-

non and the fragile state of many diabetic hyperadrenal cats, I typically use only one dexamethasone suppression test protocol (0.1 mg/kg dexamethasone administered intravenously; blood obtained before and 4 and 8 hours after dexamethasone administration) when evaluating the pituitary-adrenocortical axis in cats. An 8-hour postdexamethasone serum cortisol concentration less than 1.0 ug/dl is suggestive of a normal pituitary-adrenocortical axis, values between 1.0 and 1.4 ug/dl are inconclusive, and values greater than 1.4 Jg/dl are supportive of the diagnosis of hyperadrenocorticism. The higher the 8-hour post-dexamethsone serum cortisol concentration above 1.4 ug/dl, the more supportive the test is for the diagnosis of hyperadrenocorticism. Similarly, a serum cortisol concentration greater than 1.4 µg/dl at the 4-hour postdexamethasone blood sampling time adds further support for the diagnosis of hyperadrenocorticism (Fig. 53-19). Whenever the 4-hour post-dexamethasone cortisol value is less than 1.4 ug/dl (especially less than 1.0 ug/



#### FIG 53-18

**A,** A 15-year-old cat with pituitary-dependent hyperadrenocorticism (PDH), insulin-resistant diabetes mellitus, and feline fragile skin syndrome. Note the torn skin over the back of the neck that occurred while the cat was being restrained during a physical examination. **B,** A 12-year-old cat with hyperadrenocorticism and severe insulin-resistant diabetes mellitus. This cat weighed 2.2 kg and was receiving 25 units of regular insulin three times a day with no glucose-lowering effect. Note the emaciated appearance, presumably resulting from protracted poor glycemic control, alopecia, severe dermal and epidermal atrophy, and lesions resulting from easily torn skin (arrow). **C,** A 17-year-old cat with PDH and insulin-resistant diabetes mellitus. Note the emaciated appearance of the cat, the enlarged abdomen (pot-belly appearance), and absence of hair growth on the ventral abdomen, which had been shaved for an abdominal ultrasound 10 months before presentation.

dl), the test results should be considered consistent with, but not definitively diagnostic of, hyperadrenocorticism and the clinician must rely on the clinical signs, physical examination findings, and results of other diagnostic tests to help establish the diagnosis. Results of the dexamethasone suppression test should never constitute the sole evidence for hyperadrenocorticism in cats.

# Adrenocorticotropic Hormone Stimulation Test

The peak increase in the post-ACTH serum cortisol concentration occurs earlier in cats than in dogs, and serum cortisol concentrations can approach baseline values by 1 or 2 hours

after the administration of synthetic or porcine ACTH, respectively. Whenever porcine ACTH gel is used, blood samples for cortisol determination should be obtained 1 and 2 hours after its administration. Whenever synthetic ACTH is used, blood samples should be obtained 30 minutes and 1 hour after its administration. The reference range for peak post-ACTH serum cortisol concentration is 5 to 15 µg/dl. Post-ACTH serum cortisol concentrations greater than 15 µg/dl are suggestive of hyperadrenocorticism. The sensitivity of the ACTH stimulation test in identifying hyperadrenocorticism is low in cats. Fewer than 50% of cats with hyperadrenocorticism confirmed at necropsy have abnormal ACTH stimulation test results consistent with the disease.



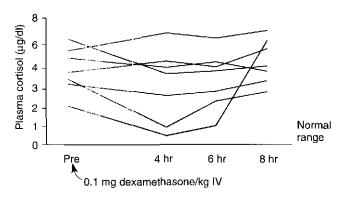
**TABLE 53-4** 

# Diagnostic Tests to Assess the Pituitary-Adrenocortical Axis in Cats with Suspected Hyperadrenocorticism

TEST	PURPOSE	PROTOCOL	RESULTS	INTERPRETATION
Urine cortisol: creatinine ratio	Rule out Cushing's syndrome	Urine collected at home	Normal	Not supportive of Cushing's syndrome
	•,		Increased	Additional tests for Cushing's indicated
			8-hr post-dexamethasone:	
Dexamethasone	Diagnose Cushing's	0.1 mg dexamethasone/kg IV;	<1.0 μg/dl	Normal
suppression test	syndrome	serum pre- and 4 and 8 hr post-dexamethasone	1.0-1.5 μg/dl	Nondiagnostic
			>1.5 µg/dl and	Suggestive†
			4 hr <1.5 μg/dl	Strongly
			>1.5 μg/dl and	suggestive‡
			4 hr >1.5 μg/dl	
				risol concentration:
ACTH stimulation	Diagnose Cushing's	2.2 IU of ACTH gel*/kg IM;	>20 μg/dl	Strongly suggestive
	syndrome	serum pre- and 1 and 2 hrs	15-20 μg/dl	Suggestive
		post-ACTH or 0.125 mg of	5-15 μg/dl	Normal
		synthetic ACTH*/cat IM; serum pre- and 30 and 60 min post-ACTH	<5 μg/dl	latrogenic Cushing's syndrome
Endogenous ACTH	Differentiate	Plasma sample obtained	<2 pmol/L	ATH
	PDH from ATH	between 8 and 10 AM	2-10 pmol/L	Nondiagnostic
		Special handling required	>10 pmol/L	PDH

ACTH, Adrenocorticotropic hormone; IM, intramuscular; PDH, pituitary-dependent hyperadrenocorticism; ATH, adrenal tumor causing hyperadrenocorticism.

<sup>‡</sup>Strongly suggestive of hyperadrenocorticism.



# FIG 53-19

Dexamethasone suppression test results in seven cats with histologically confirmed hyperadrenocorticism. Blood for the cortisol determination was drawn before and 4, 6, and 8 hours after the intravenous administration of 0.1 mg of dexamethasone/kg body weight. In most cats the plasma cortisol concentration remained more than 1.4  $\mu$ g/dl throughout the test—results that are very consistent with a diagnosis of hyperadrenocorticism.

# Endogenous Plasma Adrenocorticotropic Hormone Concentration

The endogenous plasma ACTH concentration test is discussed on p. 824. The reference range for baseline plasma ACTH concentrations in cats is 2 to 13 pmol/l. Undetectable plasma endogenous ACTH concentrations (less than 2 pmol/L) are consistent with ATH, endogenous ACTH concentrations greater than 10 pmol/l are consistent with PDH, and endogenous ACTH concentrations between 2 and 10 are nondiagnostic.

# Diagnosis

Hyperadrenocorticism is diagnosed on the basis of history; findings on physical examination; results of routine blood and urine tests, abdominal ultrasonography, and tests of the pituitary-adrenocortical axis; and the clinician's index of suspicion for the disease. Ideally, all diagnostic tests performed in the assessment of a cat with suspected hyperadrenocorticism should be abnormal. Discordant test results raise doubt regarding the diagnosis. False-positive and false-negative results occur with all of the diagnostic tests used to assess the pituitary-adrenocortical axis. Although normal UCCR and dexamethasone suppression test results are inconsistent with a diagnosis of hyperadrenocorticism,

<sup>\*</sup>ACTH gel: Acthar Gel, Questcor Pharmaceuticals; Synthetic ACTH: Cortrosyn, Amphastar Pharmaceuticals.

<sup>†</sup> Suggestive of hyperadrenocorticism.

abnormal results of these tests do not by themselves confirm the diagnosis. If there is doubt or uncertainty about the diagnosis, therapy for hyperadrenocorticism should be withheld and the cat reevaluated 1 to 2 months later.

#### **Treatment**

Treatment of hyperadrenocorticism is problematic in cats, primarily because a reliable medical treatment for PDH has not been identified. Trilostane is the current treatment of choice because other treatments, such as mitotane, ketoconazole, and the enzyme inhibitor metyrapone, are ineffective or only transiently effective. The trilostane treatment and monitoring protocols are similar for dogs and cats (see p. 827). The initial dose is 1 to 2 mg/kg of body weight once daily. Adjustments in the dose and frequency of administration are based on clinical response and results of the ACTH stimulation test, UCCR, and serum electrolyte concentrations. In general, twice-daily dosing provides better control than once-daily dosing and should be the initial adjustment

in cats that remain symptomatic at the starting dose given once daily. In one study by Neiger et al. (2004), three cats with PDH were still alive 6, 11, and 20 months after starting trilostane therapy at 30 mg/cat once a day.

Aminoglutethimide (Cytadren, 30 mg/cat, administered orally q12h; Ciba-Geigy Pharmaceuticals) inhibits the conversion of cholesterol to pregnenolone, thereby reducing cortisol hypersecretion. Aminoglutethimide has been used successfully in controlling clinical signs of hyperadrenocorticism and hyperprogesteronemia in cats with progesterone-secreting tumors (Fig. 53-20) and appears to maintain its efficacy for a relatively prolonged period of time (i.e., months). Cobalt irradiation may be tried in cats with pituitary macrotumor, although clinical signs of hypercortisolemia may persist despite shrinkage of the tumor.

Adrenalectomy is the treatment of choice for ATH, and bilateral adrenolectomy is also an effective treatment for PDH. Medical treatment with trilostane is usually necessary for 4 to 6 weeks before adrenalectomy to reverse the catabolic



#### FIG 53-20

**A**, A 9-year-old male castrated domestic long-haired cat with a 2-year history of poorly controlled diabetes mellitus, failure of hair to regrow after clipping 1 year before presentation, and recent development of feline fragile skin syndrome. Diagnostic evaluation revealed an adrenocortical tumor, increased serum progesterone concentration, and suppression of the pituitary-adrenocortical axis on adrenocorticotropic hormone stimulation and dexamethasone suppression testing. A progesterone-secreting adrenocortical tumor was suspected. **B**, Five weeks after initiating treatment with aminoglutethemide. Feline fragile skin syndrome was resolving, hair was growing, and gynecomastia had developed. The serum progesterone concentration had decreased from a pretreatment value of 4.7 ng/ml to less than 1 ng/ml. **C**, Four months after adrenalectomy. Insulin-requiring diabetes mellitus had resolved.

state of the cat, improve skin fragility and wound healing, and decrease the potential for perioperative complications. The surgical approach and medical management during and after surgery are similar to those used in dogs (see p. 828). Treatment for hypoadrenocorticism should begin immediately after bilateral adrenalectomy and include injectable desoxycorticosterone pivalate (DOCP, 2.2 mg/kg, administered subcutaneously every 25 days initially; Percoten-V; Novartis Pharmaceuticals) or fludrocortisone acetate (Florinef, 0.05 mg/cat, administered orally q12h initially; ER Squibb & Sons) and prednisolone (1.0 to 2.5 mg once daily). Subsequent adjustments in the dose of DOCP or fludrocortisone acetate should be based on periodically measured serum electrolyte concentrations (see p. 840). Insulin therapy can be discontinued in approximately 50% of cats once hyperadrenocorticism is eliminated, and diabetes is easier to control using less insulin in the remaining cats.

# **Prognosis**

The prognosis is guarded to poor. Untreated hyperadrenal cats die within months after the diagnosis has been established because of the deleterious effects of chronic hypercortisolism and insulin-resistant diabetes mellitus on skin integrity and on immune and cardiovascular function and as a result of progressive weight loss leading to severe cachexia. The effectiveness of trilostane remains to be determined. Unilateral (ATH) or bilateral (PDH) adrenalectomy has the potential for excellent success; however, success depends, in part, on correction of the debilitated state and skin fragility with medical treatment before surgery, involvement of a surgeon with expertise in adrenal surgery, avoidance of perioperative complications, and the client's commitment to managing the iatrogenic adrenal insufficiency after bilateral adrenalectomy. Periodic evaluation of serum electrolytes and review of the treatment protocol are important. An addisonian crisis occurred months after surgery in several cats treated in our clinic and was believed to be responsible for the death of some.

# **HYPOADRENOCORTICISM**

# Etiology

Hypoadrenocorticism is a deficiency of mineralocorticoids, glucocorticoids, or both. Primary adrenocortical insufficiency (Addison's disease) involving a deficiency of both mineralocorticoid and glucocorticoid secretion is the most common. The etiology of primary hypoadrenocorticism is usually classified as idiopathic because the cause of the disease is not obvious and necropsies are usually done years after the diagnosis is established, at which time idiopathic atrophy of all layers of the adrenal cortex is the most frequent histopathologic finding. Immune-mediated destruction of the adrenal cortices is believed to occur in most dogs and cats with idiopathic adrenal insufficiency; lymphocytes, plasma cells, and fibrosis are common findings in animals that undergo necropsy near the time of diagnosis. Bilateral destruction of the

adrenal cortex by neoplasia (e.g., lymphoma), granulomatous disease, hemorrhagic infarction, arterial thrombosis, or drugs such as mitotane and trilostane can also cause primary adrenocortical insufficiency. For clinical signs to develop, it is believed that at least 90% of the adrenal cortices must be destroyed. The zones of the adrenal cortices are usually damaged at about the same rate, with aldosterone and glucocorticoid deficiency typically occurring in tandem. Destruction is progressive, ultimately leading to complete loss of adrenocortical function. Dogs and cats typically have complete loss of adrenocortical function at the time hypoadrenocorticism is diagnosed. A partial deficiency syndrome characterized by inadequate adrenal reserve may occur initially, with clinical signs manifested only during times of stress such as boarding, travel, and surgery. As destruction of the adrenal cortex progresses, hormone secretion becomes inadequate even under nonstressful conditions and a true metabolic crisis occurs without any obvious inciting event.

Mineralocorticoids (i.e., aldosterone) control sodium, potassium, and water homeostasis. In the setting of primary adrenocortical insufficiency, a loss of aldosterone secretion results in impaired renal conservation of sodium and chloride and the excretion of potassium, leading to the development of hyponatremia, hypochloremia, and hyperkalemia. The inability to retain sodium and chloride reduces extracellular fluid volume, leading to progressive development of hypovolemia, hypotension, a reduced cardiac output, and decreased perfusion of the kidneys and other tissues. Hyperkalemia has a deleterious effect on cardiac function, causing decreased myocardial excitability, an increased myocardial refractory period, and slowed conduction. A concurrent glucocorticoid deficiency typically results in gastrointestinal tract signs (e.g., anorexia, vomiting, diarrhea, weight loss) and changes in mental status (e.g., lethargy). One of the hallmark signs of hypocortisolism is impaired tolerance to stress, and clinical signs often become more pronounced when the animal is placed in stressful situations.

Some dogs and cats with hypoadrenocorticism present to the veterinarian with clinical signs of glucocorticoid deficiency but serum electrolyte concentrations that are within the reference range at initial presentation. A deficiency in glucocorticoid but not mineralocorticoid secretion is referred to as atypical hypoadrenocorticism and is discussed on p. 841. Glucocorticoid deficiency resulting from pituitary dysfunction is also called secondary hypoadrenocorticism. Destructive lesions in the pituitary gland or hypothalamus, the long-term administration of exogenous glucocorticoids, and idiopathic loss of function are the most common causes of secondary adrenal insufficiency. Naturally occurring, isolated hypoaldosteronism is rare in dogs and cats.

#### **Clinical Features**

# **SIGNALMENT**

Hypoadrenocorticism is typically a disease of young to middle-aged female dogs, with a median age of 4 to 6 years and a range of 2 months to 12 years. Dogs with glucocorti-

coid-deficient hypoadrenocorticism tend to be older at the time of diagnosis than dogs with mineralocorticoid and glucocorticoid deficient hypoadrenocorticism. Breeds reported to be at increased risk for hypoadrenocorticism are listed in Box 53-6. Hypoadrenocorticism is rare in cats. There is no apparent sex-related predisposition in cats, although it tends to occur in young to middle-aged cats (average age 6 years). Hypoadrenocorticism can, however, occur in aged dogs and cats as well.

# CLINICAL SIGNS AND PHYSICAL **EXAMINATION FINDINGS**

Clinical signs and physical examination findings are listed in Box 53-7. The most common clinical manifestations are related to alterations in the gastrointestinal tract and mental status and include lethargy, anorexia, vomiting, and weight loss. Weakness is also a common client complaint. Additional physical examination findings may include dehydration, bradycardia, weak femoral pulses, and abdominal pain. Hyperkalemia and hypoadrenocorticism should be suspected in an animal with bradycardia and signs consistent with hypovo-



BOX 53-6

# Breeds at Increased Risk for Hypoadrenocorticism

Portuguese Water Dog† Standard Poodlet Nova Scotia Duck Tolling Retriever† Bearded Collie\* Leonberger‡ Great Dane‡

Rottweiler‡

West Highland White Terrier‡ Soft Coated Wheaten Terrier‡

- \* Highly heritable but mode of inheritance undetermined.
- † Autosomal recessive mode of inheritance strongly suspected.
- ‡Genetic predisposition suspected.



BOX 53-7

# Clinical Signs Caused by Hypoadrenocorticism in Dogs and Cats

DOGS	CATS
Lethargy* Anorexia* Vomiting* Weakness* Diarrhea Weight loss Shivering Polyuria, polydipsia Abdominal pain	Lethargy* Anorexia* Weight loss* Vomiting Polyuria, polydipsia

<sup>\*</sup> Common.

lemia. Bradycardia by itself, however, is not pathognomonic for hypoadrenocorticism, especially in an otherwise healthy dog. Similarly, dogs with hypoadrenocorticism can have normal heart rates. Polyuria and polydipsia are rarely presenting signs, although they may surface during the taking of a complete history.

Clinical signs are often vague and easily ascribed to more common disorders involving the gastrointestinal and urinary tracts. Observant clients may occasionally describe an illness with a waxing-waning or episodic course; however, this bit of historic information is the exception rather than the rule. Most dogs with hypoadrenocorticism are first seen because of progressive problems that vary in severity, depending on the degree of stress and the adrenocortical reserve.

If hyponatremia and hyperkalemia become severe, the resultant hypovolemia, prerenal azotemia, and cardiac arrhythmias may result in an addisonian crisis. The clinical manifestations are as previously described; the only difference is in the severity of signs. In severe cases the animal may be presented in shock and be moribund. An addisonian crisis must be differentiated from other life-threatening disorders, such as diabetic ketoacidosis, necrotizing pancreatitis, acute hepatitis, septic peritonitis, and acute renal failure.

#### **CLINICAL PATHOLOGY**

Several abnormalities may be identified on a CBC, serum biochemistry panel, and urinalysis (Box 53-8). Hyperkalemia, hyponatremia, and hypochloremia are the classic electrolyte alterations in animals with adrenal insufficiency and



BOX 53-8

Clinicopathologic Abnormalities Associated with Primary Hypoadrenocorticism in Dogs and Cats

#### Hemogram

Nonregenerative anemia

- Neutrophilic leukocytosis
- ± Mild neutropenia
- ± Eosinophilia
- ± lymphocytosis

#### **Biochemistry Panel**

Hyperkalemia

Hyponatremia

Hypochloremia

Prerenal azotemia

Hyperphosphatemia

- ± Hypercalcemia
- ± Hypoglycemia
- ± Hypoalbuminemia
- ± Hypocholesterolemia

Metabolic acidosis (low total CO<sub>2</sub>, HCO<sub>3</sub>-)

#### Urinalysis

Isosthenuria to hypersthenuria

are perhaps the most important evidence ultimately used to establish a diagnosis of hypoadrenocorticism. Serum sodium concentrations vary from normal to as low as 105 mEq/L (mean 128 mEq/L), and serum potassium concentrations vary from normal to greater than 10 mEq/L (mean 7.2 mEq/L). The sodium: potassium ratio reflects changes in these electrolyte concentrations in serum and has been frequently used as a diagnostic tool to identify adrenal insufficiency. The normal ratio varies between 27:1 and 40:1. Values are often less than 27 and may be less than 20 in animals with primary adrenal insufficiency.

Electrolyte alterations by themselves can be misleading. Normal serum electrolyte concentrations do not rule out adrenal insufficiency. Electrolyte abnormalities may not be evident in the early stages of the disorder, when clinical signs result from glucocorticoid deficiency, and do not develop with secondary adrenal insufficiency caused by pituitary failure. Alternatively, other disorders can cause alterations in serum electrolyte concentrations that mimic adrenal insufficiency, most notably disorders involving the hepatic, gastrointestinal, and urinary systems (see Boxes 55-2 and 55-3). For most disorders a thorough history and physical examination, together with a critical evaluation of results of the CBC, serum biochemistry panel, and urinalysis, allow the clinician to prioritize the potential differential diagnoses. Important clues for hypoadrenocorticism include lack of a stress leukogram in a sick dog or cat and identification of hypoalbuminemia, hypocholesterolemia, hypoglycemia, or a combination of these on the serum biochemistry panel.

The most challenging aspect of diagnosis is the differentiation between acute renal failure and primary adrenal insufficiency. The azotemia of adrenal insufficiency occurs secondary to reduced renal perfusion and an associated decrease in glomerular filtration rate after the onset of hypovolemia and hypotension. A compensatory increase in urine specific gravity to greater than 1.030 allows prerenal azotemia to be differentiated from primary renal azotemia and therefore adrenal insufficiency to be differentiated from acute renal failure, respectively.

Unfortunately, many hypoadrenal dogs and cats have an impaired ability to concentrate urine because of chronic urinary sodium loss, depletion of the renal medullary sodium content, loss of the normal medullary concentration gradient, and impaired water resorption by the renal collecting tubules. As a result, some hypoadrenal dogs and cats with prerenal azotemia have urine specific gravities in the isosthenuric range (i.e., 1.007 to 1.015). Fortunately, the initial therapy for acute renal failure is similar to that used for adrenal insufficiency. Ultimately, the differentiation between these two disorders must rely on testing of the pituitary-adrenocortical axis and the animal's response to initial fluid and other supportive therapy.

## **ELECTROCARDIOGRAPHY**

Hyperkalemia depresses cardiac conduction and causes characteristic alterations on an electrocardiogram (ECG; see Box 55-4). The severity of the ECG abnormalities correlates with the severity of hyperkalemia. The ECG can be used as a diagnostic tool to identify and estimate the severity of hyperkalemia and as a therapeutic tool to monitor changes in the blood potassium concentration during therapy.

#### DIAGNOSTIC IMAGING

Hypoadrenal dogs and cats with severe hypovolemia often have microcardia, a descending aortic arch that is flattened and has a decreased diameter, and a narrow caudal vena cava, as seen on lateral thoracic radiographs. These findings are a crude means of evaluating the degree of hypovolemia and hypotension. Concurrent generalized megaesophagus may be evident and may resolve in response to treatment for the hypoadrenocorticism. Abdominal ultrasonography may reveal small adrenal glands (i.e., maximum width less than 0.3 cm), a finding suggestive of adrenocortical atrophy. However, finding normal-size adrenal glands does not rule out hypoadrenocorticism.

# Diagnosis

Hypoadrenocorticism is often tentatively diagnosed on the basis of the history; physical examination findings; clinicopathologic findings; and, in the case of primary adrenal insufficiency, identification of appropriate electrolyte abnormalities. Results of an ACTH stimulation test confirm the diagnosis (see Table 53-2). Baseline serum cortisol concentrations of greater than 2 µg/dl are inconsistent with the diagnosis of hypoadrenocorticism, but baseline serum cortisol concentrations of 2 µg/dl or less do not confirm the diagnosis. UCCRs are not reliable for confirming the diagnosis. One major criterion is used in confirming the diagnosis of adrenal insufficiency: a post-ACTH serum cortisol concentration less than 2 µg/dl (Fig. 53-14). A post-ACTH serum cortisol concentration of 4 µg/dl or greater is inconsistent with the diagnosis of adrenal insufficiency. Post-ACTH serum cortisol values between 2 and 4 µg/dl are equivocal and may occur with relative adrenal insufficiency-a syndrome defined as inadequate production of cortisol in relation to increased demand during periods of critical illness such as sepsis. Prolonged or excessive inflammatory cytokine activity suppresses pituitary and adrenal function in humans and possibly in dogs as well. In a recent study by Burkitt et al. (2007), dogs with severe sepsis had a suppressed response of the adrenal cortex to exogenously administered ACTH, an increase in serum cortisol concentration of less than 3 µg/dl after ACTH administration, and resolution of the relative adrenal insufficiency after resolution of the illness.

Results of the ACTH stimulation test do not distinguish dogs and cats with naturally occurring primary adrenal insufficiency from those with secondary insufficiency resulting from pituitary failure, dogs and cats with secondary insufficiency resulting from prolonged iatrogenic glucocorticoid administration, or dogs with primary adrenocortical destruction caused by mitotane or trilostane overdosing.



Differentiation of Primary Versus Secondary Hypoadrenocorticism

	PRIMARY HYPOADRENOCORTICISM	PRIMARY ATYPICAL HYPOADRENOCORTICISM	SECONDARY HYPOADRENOCORTICISM
Serum electrolytes	Hyperkalemia Hyponatremia	Normal	Normal
ACTH stimulation test Post-ACTH cortisol Post-ACTH aldosterone Endogenous ACTH	Decreased Decreased Increased	Decreased Normal Increased	Decreased Normal Decreased

ACTH, Adrenocorticotropic hormone.

Concurrent abnormal serum electrolyte concentrations imply the existence of primary adrenal insufficiency and the need for mineralocorticoid and glucocorticoid replacement therapy. Normal serum electrolyte concentrations do not differentiate between primary hypoadrenocorticism that progresses and primary hypoadrenocorticism that does not progress to mineralocorticoid deficiency or between primary hypoadrenocorticism and secondary hypoadrenocorticism (see the section on atypical hypoadrenocorticism). If secondary hypoadrenocorticism can be documented, only glucocorticoid replacement therapy is indicated. Primary and atypical or secondary hypoadrenocorticism can be differentiated prospectively by periodically measuring serum electrolyte concentrations, by measuring baseline endogenous ACTH concentration, or by measuring plasma aldosterone concentrations during the ACTH stimulation test (Table 53-5). In theory, measurement of plasma aldosterone concentration should be helpful in distinguishing between the various forms of adrenal insufficiency. Unfortunately, there is no clear demarcation in plasma aldosterone concentrations between these groups of dogs.

#### **Treatment**

The aggressiveness of therapy depends on the clinical status of the animal and the nature of the insufficiency (i.e., glucocorticoid or mineralocorticoid or both). Many dogs and cats with primary adrenal insufficiency are presented in varying stages of an acute addisonian crisis, requiring immediate, aggressive therapy. In contrast, dogs and cats with isolated glucocorticoid deficiency often have a chronic course that poses more of a diagnostic than a therapeutic challenge.

# THERAPY FOR ACUTE ADDISONIAN CRISIS

An acute addisonian crisis involves both a mineralocorticoid and a glucocorticoid deficiency. The treatment of acute primary adrenal insufficiency is directed toward correcting hypotension, hypovolemia, electrolyte imbalances, and metabolic acidosis; improving vascular integrity; and providing



#### Initial Treatment for Acute Addisonian Crisis

#### **Fluid Therapy**

Type: 0.9% saline solution
Rate: 40 to 80 ml/kg/h IV initially
Potassium supplementation: contraindicated

Dextrose: 5% dextrose infusion (100 ml of 50% dextrose

per liter of fluids)

# **Glucocorticoid Therapy**

Dexamethasone sodium phosphate, 0.5 to 1.0 mg/kg IV, repeat q12h at dosage of 0.05 to 0.1 mg/kg in IV fluids until oral prednisone can be administered.†

Alternatively, hydrocortisone hemisuccinate or hydrocortisone phosphate,\* 2 to 4 mg/kg IV or prednisolone sodium succinate,\* 4 to 20 mg/kg IV, then dexamethasone sodium phosphate, 0.05 to 0.1 mg/kg in IV fluids q12h.

#### Mineralocorticoid Therapy

Desoxycorticosterone pivalate (DOCP; Novartis), 2.2 mg/kg IM q25 days initially.

#### **Bicarbonate Therapy**

Indicated if  $HCO_3$  <12 mEq/L or total venous  $CO_2$  <12 mmol/L or animal is severely ill. mEq  $HCO_3$  = body weight (kg) × 0.5 × base deficit (mEq/L); if base deficit unknown, use 10 mEq/L. Add one quarter of calculated  $HCO_3$  dose to IV fluids and administer over 6 hours. Repeat only if plasma  $HCO_3$  remains <12 mEq/L.

IV, Intravenous; IM, intramuscular.

\* Assays to measure cortisol may measure hydrocortisone and prednisolone, interfering with interpretation of the adrenocorticotropic hormone stimulation test result.

† Higher doses of glucocorticoids may be required if the dog or cat is in shock.

an immediate source of glucocorticoids (Box 53-9). Because death resulting from hypoadrenocorticism is often attributed to vascular collapse and shock, rapid correction of hypovolemia is the first and most important therapeutic priority. Physiologic saline solution is the IV fluid of choice because it aids in correcting hypovolemia, hyponatremia, and hypochloremia. Hyperkalemia is reduced by simple dilution and by improved renal perfusion. Potassium-containing fluids (see Table 55-2) are relatively contraindicated but should be used in lieu of not giving IV fluids at all.

If hypoglycemia is suspected or known to be present, 50% dextrose should be added to the IV fluids to produce a 5% dextrose solution (i.e., 100 ml of 50% dextrose per liter of fluids). The addition of dextrose to isotonic solutions produces a hypertonic solution that ideally should be administered through a central vein to minimize phlebitis.

Dogs and cats with acute adrenal insufficiency usually have a mild metabolic acidosis that does not require therapy. Fluid therapy alone corrects the mild acidosis as hypovolemia lessens and tissue perfusion and glomerular filtration rate improve. If the total venous carbon dioxide or the serum bicarbonate concentration is less than 12 mmol/L or 12 mEq/L, respectively, conservative bicarbonate therapy is indicated. In a severely ill animal in which laboratory results are not yet known, a base deficit of 10 mEq/L can be assumed to be present. The milliequivalents of bicarbonate needed to correct the acidosis can be determined from the following equation:

# Bicarbonate deficit (mEq/L) = Body weight (kg) $\times$ 0.5 $\times$ Base deficit (mEq/L)

One fourth of the calculated bicarbonate dose should be administered in the IV fluids during the initial 6 to 8 hours of therapy. The acid-base status of the animal should be reassessed at the end of this time. Rarely, a dog or cat may require additional parenterally administered sodium bicarbonate.

Sodium bicarbonate therapy helps correct the metabolic acidosis and also decreases the serum potassium concentration. The intracellular movement of potassium ions after bicarbonate administration, in conjunction with the dilutional effects of saline fluid therapy and improved renal perfusion, is quite effective in lowering the serum potassium concentration and returning any ECG abnormalities toward normal. Additional therapy to rapidly correct life-threatening hyperkalemia is rarely needed (see Box 55-3).

Glucocorticoid and mineralocorticoid therapy is also indicated in the initial management of an acute addisonian crisis. Ideally, glucocorticoids should not be given until after completion of the ACTH stimulation test. IV infusion of saline is usually sufficient therapy during the initial 1 or 2 hours while the ACTH stimulation test is being completed. Dexamethasone does not interfere with the cortisol assay and can be used if glucocorticoid therapy cannot be delayed. Our glucocorticoid of choice for treating an acute addisonian crisis is dexamethasone sodium phosphate, given intra-

venously at an initial dosage of 0.5 to 1.0 mg/kg and repeated q12h at a dose of 0.05 to 0.1 mg/kg in the IV solution until oral medication can be safely given. Rapid-acting, water-soluble glucocorticoids such as hydrocortisone sodium succinate, hydrocortisone hemisuccinate, hydrocortisone phosphate, and prednisolone sodium succinate may be measured by the cortisol assay, causing falsely increased cortisol results, and should not be administered until after the ACTH stimulation test is completed. We do not routinely use these glucocorticoids for treating acute adrenal insufficiency.

Currently available mineralocorticoid supplements include DOCP (Percorten-V; Novartis Pharmaceuticals) and fludrocortisone acetate (Florincf; ER Squibb & Sons). Both are intended for the long-term maintenance therapy of primary adrenal insufficiency. Injectable DOCP is the preferred mineralocorticoid for the treatment of a sick dog or cat suspected of having adrenal insufficiency. The drug is initially administered at a dose of 2.2 mg/kg intramuscularly or subcutaneously every 25 days initially. In an animal in an emergency hypoadrenal crisis, the drug should be administered intramuscularly. The IV administration of saline solution and the intramuscular administration of DOCP correct electrolyte abnormalities in most hypoadrenal animals within 24 hours. There are no adverse reactions to a single injection of DOCP administered to dogs subsequently shown to have normal adrenocortical function. Atrial natriuretic peptide provides natural protection against hypernatremia. Fludrocortisone acetate is also an effective treatment. However, it is available only in tablet form, and most dogs and cats are too ill to receive oral therapy initially.

Most dogs and cats with acute adrenal insufficiency show dramatic clinical and biochemical improvement within 24 to 48 hours. Over the ensuing 2 to 4 days the animal should be gradually switched from IV fluids to oral water and food. Maintenance mineralocorticoid and glucocorticoid therapy should be initiated. If the animal fails to make this transition smoothly, persistent electrolyte imbalance, insufficient glucocorticoid supplementation, a concurrent endocrinopathy (e.g., hypothyroidism), or concurrent illness (most notably renal damage or pancreatitis resulting from poor perfusion and hypoxia caused by adrenal insufficiency) should be suspected.

# MAINTENANCE THERAPY FOR PRIMARY ADRENAL INSUFFICIENCY

Mineralocorticoids and usually glucocorticoids are required for maintenance of the dog or cat with primary adrenal insufficiency. The preferred mineralocorticoid supplementation is injectable DOCP, which slowly releases the hormone at a rate of 1 mg/day/25 mg suspension. The initial dosage is 2.2 mg/kg body weight, given intramuscularly or subcutaneously every 25 days. Subsequent adjustments are based on results of serum electrolyte concentrations, which are initially measured 12 and 25 days after each of the first two or three DOCP injections. If the dog or cat has hyponatremia or hyperkalemia (or both), on day 12 the next dose should be increased by approximately 10%. If the day 12 electrolyte

profile is normal but the day 25 profile is abnormal, the interval between injections should be decreased by 48 hours. DOCP is very effective in normalizing serum electrolyte concentrations. The only adverse reaction is polyuria and polydipsia that improve after reduction of the DOCP dose. Most dogs (and presumably cats) receiving DOCP also require a low dose of glucocorticoids (prednisone, 0.25 mg/kg q12h initially).

Drawbacks to DOCP are problems with availability and the inconvenience and expense associated with the need to make monthly visits to the veterinarian for the injection. To minimize the inconvenience and expense, the client is routinely taught to give the injection subcutaneously at home. Every third or fourth treatment, the client should bring the dog or cat into the clinic for a complete physical examination, measurement of serum electrolyte concentrations, and administration of DOCP to ensure that problems with the administration of DOCP have not developed. Once the dog or cat is healthy and serum electrolyte concentrations are stable, the amount of DOCP administered can be decreased by 10% increments initially and the frequency of DOCP administration can be shortened to every 21 days to allow lower doses of DOCP to be administered (typically about 1.5 mg/kg/injection), thereby decreasing the expense of treatment. The goal is to identify the lowest dosage of DOCP that maintains the health of the dog or cat and keeps serum electrolyte concentrations in the reference

Fludrocortisone acetate (Florinef) is another commonly used mineralocorticoid supplement. The initial dose is 0.02 mg/kg/day, divided into two doses, and administered orally. Subsequent adjustments in the dose are based on serum electrolyte concentrations, which are initially assessed every 1 to 2 weeks. The goal is to reestablish normal serum sodium and potassium concentrations. The dose of fludrocortisone acetate must typically be increased during the first 6 to 18 months of therapy. This increasing need may reflect the continuing destruction of the adrenal cortices. After this time the dose usually plateaus and remains relatively stable.

The major drawbacks to oral therapy with fludrocortisone acetate are the wide range in the doses required to control serum electrolyte concentrations; the development of polyuria, polydipsia, and incontinence in some dogs (presumably caused by the potent glucocorticoid activity of this drug); resistance to the effects of the drug, which has been observed in some animals; and persistent mild hyperkalemia and hyponatremia in some animals. Ineffectiveness of fludrocortisone acetate should be suspected when clients report that their pet is "just not right" and hyponatremia and hyperkalemia persist despite high dosages of the mineralocorticoid supplement. The concurrent administration of hydrocortisone hemisuccinate or oral salt may help alleviate the electrolyte derangements in dogs and cats in which fludrocortisone acetate by itself is not completely effective. Alternatively, switching to DOCP should be considered.

Glucocorticoid supplementation is initially indicated for all dogs and cats with primary adrenal insufficiency. Prednisone (dogs) and prednisolone (cats) is given at an initial dose of 0.25 mg/kg twice a day orally. Over the ensuing 1 to 2 months the dose of prednisone or prednisolone should gradually be reduced to the lowest amount given once a day that still prevents signs of hypocortisolism. Approximately 50% and fewer than 10% of dogs receiving fludrocortisone and DOCP, respectively, ultimately do not require glucocorticoid medication, except during times of stress. All clients should have glucocorticoids available to administer to their dogs and cats in times of stress. Veterinarians should also be aware of the increased glucocorticoid requirements of hypoadrenal dogs and cats undergoing surgery or during times of illness with a nonadrenal-related disease. The glucocorticoid dose being administered should be doubled on days when increased stress is anticipated.

The most common reason for persistence of clinical signs despite appropriate treatment is inadequate glucocorticoid supplementation. When healthy and in a nonstressed environment, dogs and cats with adrenal insufficiency typically require small amounts of prednisone or prednisolone, if any. However, when stressed or ill, these same animals may require large amounts of prednisone or prednisolone (i.e., 0.25 to 0.5 mg/kg) given twice a day. Failure to provide adequate amounts of glucocorticoids can lead to persistent and worsening lethargy, inappetence, and vomiting. The amount of prednisone or prednisolone required to offset the deleterious effects of stress and illness is variable and unpredictable. As such, it is always better to err on the high end of the dosage range and then gradually decrease the dosage over the ensuing weeks.

#### **Prognosis**

The prognosis in dogs and cats with adrenal insufficiency is usually excellent. The most important factors in determining an animal's long-term response to therapy are client education about the disease and client dedication to treatment. If there is good client-veterinarian communication, if frequent rechecks are performed, and if clients are conscientious about carrying out therapy, dogs and cats with adrenal insufficiency can have a normal life expectancy.

#### ATYPICAL HYPOADRENOCORTICISM

Some dogs and cats with hypoadrenocorticism present to the veterinarian with clinical signs of glucocorticoid deficiency but with serum electrolyte concentrations that are within the reference range at initial presentation. A deficiency in glucocorticoid but not mineralocorticoid secretion is referred to as *atypical hypoadrenocorticism*. Glucocorticoid deficiency may be adrenocortical in origin (primary atypical hypoadrenocorticism; most common) or may result from impaired secretion of ACTH by the pituitary gland (secondary hypoadrenocorticism). Baseline endogenous plasma ACTH concentrations are normal or increased when the primary problem is adrenal in origin and decreased when the primary problem is pituitary in origin (Table 53-5). Glucocorticoid

but not mineralocorticoid deficiency of adrenal origin may represent a dog or cat in the early stages of development of typical primary hypoadrenocorticism with destruction of the zona fasciculata more advanced than destruction of the zona glomerulosa. Mineralocorticoid deficiency and abnormal serum electrolyte concentrations develop weeks to months later. In some dogs and cats glucocorticoid deficiency does not progress to mineralocorticoid deficiency. The etiology for this form of hypoadrenocorticism is not known, although drugs such as megesterol acetate, mitotane, and trilostane are recognized causes.

Glucocorticoid deficiency resulting from pituitary dysfunction is called *secondary hypoadrenocorticism*. Destructive lesions (e.g., neoplasia, inflammation) in the pituitary gland or hypothalamus and the long-term administration of exogenous glucocorticoids are the most common recognized causes of secondary adrenal insufficiency. Adrenocortical atrophy may develop after the injectable, oral, or topical administration of glucocorticoids. Adrenal function usually returns within 2 to 4 weeks after the medication is discontinued, unless long-acting depot forms of glucocorticoids are used.

Glucocorticoid-deficient hypoadrenocorticism is usually identified during the diagnostic evaluation of dogs and cats with chronic, vague gastrointestinal clinical signs such as lethargy, anorexia, vomiting, diarrhea, and weight loss. Results of routine blood and urine tests are typically normal. Diagnosis requires an ACTH stimulation test (see p. 822). Therapy involves the administration of glucocorticoids, as previously described for the treatment of primary hypoadrenocorticism. The exception is secondary adrenal insufficiency induced by the overzealous administration of glucocorticoids, in which case therapy revolves around a gradual reduction in the dose and frequency of administration, with eventual discontinuation of the medication. Dogs and cats with secondary adrenal insufficiency should not have mineralocorticoid deficiency. The periodic measurement of serum electrolytes is advisable because primary glucocorticoid-deficient adrenal insufficiency and dogs and cats believed to have secondary adrenal insufficiency may progress to mineralocorticoid deficiency months after glucocorticoid-deficient hypoadrenocorticism is diagnosed.

#### **PHEOCHROMOCYTOMA**

#### **Etiology**

Pheochromocytoma is a catecholamine-producing tumor derived from the chromaffin cells of the adrenal medulla. Pheochromocytomas are uncommon in dogs and rare in cats. Pheochromocytomas are usually solitary, slow-growing tumors ranging in size from nodules of less than 0.5 cm in diameter to masses greater than 10 cm in diameter. Pheochromocytoma involving both adrenal glands has been reported. Pheochromocytoma should be considered a malignant tumor in dogs and cats. Pheochromocytomas commonly invade into the lumen of the adjacent phren-

icoabdominal vein and caudal vena cava, entrap and compress the caudal vena cava and phrenicoabdominal vein, or both (see Fig. 53-8). Mural invasion or luminal narrowing of the aorta, renal vessels, adrenal vessels, and hepatic veins and infiltration into the adjacent kidney and body wall may also occur. Distant sites of metastasis include the liver, lung, regional lymph nodes, bone, and CNS. Paragangliomas are tumors arising from chromaffin cells located outside of the adrenal medulla, most commonly near the sympathetic ganglia, and are rare in dogs and cats.

#### **Clinical Features**

Pheochromocytomas occur most commonly in older dogs and cats, with a median age of 11 years at the time of diagnosis in dogs. There is no apparent sex- or breed-related predisposition.

Clinical signs and physical examination findings develop as a result of the space-occupying nature of the tumor and its metastatic lesions or as a result of excessive secretion of catecholamines (Table 53-6). The most common clinical signs are generalized weakness and episodic collapse. The most common abnormalities identified during physical examination involve the respiratory, cardiovascular, and musculoskeletal systems and include excessive panting, tachypnea, tachycardia, weakness, and muscle wasting. Excess catecholamine secretion may also cause severe systemic hypertension, resulting in nasal and retinal hemorrhage and



**TABLE 53-6** 

Clinical Signs and Physical Examination Findings Associated with Pheochromocytoma in Dogs

#### **CLINICAL SIGNS**

Intermittent weakness\*
Intermittent collapsing
episodes\*
Intermittent panting\*
Intermittent tachypnea\*
Intermittent anxious
behavior\*
Polyuria, polydipsia
Lethargy
Inappetence
Vomiting
Diarrhea
Weight loss
Abdominal distension
Rear limb edema

### PHYSICAL EXAMINATION FINDINGS

No identifiable abnormalities\* Panting, tachypnea\* Weakness\* Tachycardia\* Cardiac arrhythmias Weak pulses Pale mucous membranes Muscle wasting\* Findings from systemic hypertension: Nasal hemorrhage Oral hemorrhage Retinal hemorrhage Retinal detachment Lethargy Abdominal pain Palpable abdominal mass Ascites Rear limb edema

<sup>\*</sup>Common signs and physical examination findings.

retinal detachment. Because catecholamine secretion is sporadic and unpredictable, clinical manifestations and systemic hypertension tend to be paroxysmal and are usually not evident at the time the dog is examined. Because clinical signs and physical examination findings are often vague, nonspecific, and easily associated with other disorders, pheochromocytoma is often not considered a possible differential diagnosis until an adrenal mass is identified with abdominal ultrasound.

#### **Diagnosis**

Pheochromocytoma should be on the list of differential diagnoses for dogs presenting with clinical signs suggestive of catecholamine excess, dogs with an unexpected adrenal mass identified by abdominal ultrasound, and dogs that develop unexpected problems with systemic hypertension or cardiac arrythmias during anesthesia. Pheochromocytoma may also be an unexpected or incidental finding at necropsy or may cause sudden collapse and death from a sudden, massive, and sustained release of catecholamines by the tumor.

There are no consistent abnormalities identified in the CBC, serum biochemistry panel, or urinalysis that would raise suspicion for pheochromocytoma. A history of acute or episodic collapse, the identification of appropriate respiratory and cardiac abnormalities during physical examination, the documentation of systemic hypertension, and identification of an adrenal mass by abdominal ultrasonog-

raphy are most helpful in establishing a tentative diagnosis of pheochromocytoma. Systemic hypertension may be sustained or episodic. Failure to document systemic hypertension in a dog with appropriate clinical signs does not rule out a diagnosis of pheochromocytoma.

The ultrasound identification of an adrenal mass with a normal-size contralateral adrenal gland is perhaps the most important clue for pheochromocytoma. Pheochromocytoma is one of several differentials for an adrenal mass (Table 53-7; see also the discussion of incidental adrenal mass). The primary differential diagnosis is adrenal-dependent hyperadrenocorticism. Interestingly, many of the clinical signs (e.g., panting, weakness) and blood pressure alterations seen in dogs with hyperadrenocorticism (common) are similar to those seen in dogs with pheochromocytoma (uncommon). In addition, pheochromocytoma and adrenocortical carcinoma both invade adjacent structures and cause tumor thrombi in the phrenicoabdominal vein and caudal vena cava. Kyles et al. (2003) found 6 of 11 dogs with pheochromocytoma and 6 of 28 dogs with an adrenocortical tumor had tumor thrombi. It is important to rule out adrenaldependent hyperadrenocorticism before focusing on pheochromocytoma in a dog with an adrenal mass.

Measurement of urinary catecholamine concentrations or their metabolites can strengthen the tentative diagnosis of a pheochromocytoma. Unfortunately, these tests are not commonly performed in dogs and cats. As a result, the antemortem definitive diagnosis of a pheochromocytoma ulti-

TABLE 53-7

Adrenal Tumors Reported in Dogs and Cats

	HORMONE SECRETED	SPECIES	CLINICAL SYNDROME	TESTS TO ESTABLISH DIAGNOSIS
Nonfunctional adrenal tumor	None	Dog*, Cat		Diagnosis by exclusion histopathology
Functional adreno- cortical tumor	Cortisol	Dog*, Cat	Hyperadrenocorticism Cushing's syndrome	Urine C:C ratio  Low-dose dexamethasone suppression test
	Aldosterone	Cat*, Dog	Hyperaldosteronism Conn's syndrome	Serum K <sup>+</sup> and Na <sup>+</sup> Baseline plasma aldosterone
	Progesterone	Cat*, Dog	Mimics hyperadrenocorticism	Serum progesterone
	Steroid hormone precursors			
	17-OH progesterone	Dog	Mimics hyperadrenocorticism	ACTH stimulation test— measure steroid hormone precursors
	Deoxycorticosterone	Dog	Mimics hyperaldosteronism	ACTH stimulation test— measure steroid hormone precursors
Functional adreno- medullary tumor	Epinephrine	Dog*, Cat	Pheochromocytoma	Diagnosis by exclusion Histopathology

ACTH, Adrenocorticotropic hormone.

<sup>\*</sup> Species most commonly affected.

mately relies on histologic evaluation of the surgically excised adrenal mass.

#### **Treatment**

A period of medical therapy to reverse the effects of excessive adrenergic stimulation, followed by surgical removal of the tumor, is the treatment of choice for pheochromocytoma. The success of chemotherapy and radiation therapy in humans with pheochromocytoma has been limited, and results of chemotherapy or radiation therapy for the treatment of pheochromocytoma in dogs or cats has not been reported. Mitotane is ineffective for treating tumors arising from the adrenal medulla. Long-term medical therapy is primarily designed to control excessive catecholamine secretion.

Potentially life-threatening complications are common during the perioperative period, especially during induction of anesthesia and manipulation of the tumor during surgery. The most worrisome complications include episodes of acute, severe hypertension (systolic arterial blood pressure of more than 300 mm Hg), episodes of severe tachycardia (heart rate of more than 250 beats/min) and arrhythmias, and hemorrhage. Preoperative α-adrenergic blockade is indicated to prevent severe clinical manifestations of hypertension in the preoperative period, to reverse the hypovolemia that is frequently present, and to promote a smooth anesthetic induction. Phenoxybenzamine is the drug of choice for α-adrenergic blockade. Our current protocol for the management of hypertension in dogs with pheochromocytoma includes preoperative phenoxybenzamine and intraoperative phentolamine. Our initial dosage of phenoxybenzamine is 0.5 mg/kg q12h. Unfortunately, many dogs with pheochromocytoma have episodic clinical signs and hypertension, making it difficult to adjust dosage on the basis of improvement in clinical signs and blood pressure. In addition, this dosage is often ineffective in preventing severe hypertension during surgery. Therefore we gradually increase the phenoxybenzamine dosage every few days until clinical signs of hypotension (e.g., lethargy, weakness, syncope), adverse drug reactions (e.g., vomiting), or a maximum dosage of 2.5 mg/kg q12h is attained. Surgery is recommended 1 to 2 weeks later. The drug should be continued until the time of surgery. If severe persistent tachycardia is identified, β-adrenergic antagonist therapy (e.g., propranolol: 0.2 to 1.0 mg/kg, per os, q8h; atenolol: 0.2 to 1.0 mg/kg, PO, q24h to q12h) should be used during the preoperative period but only after α-adrenergic blockade has been initiated. Complications may still occur despite prior treatment with α-adrenergic blocking drugs; close monitoring of the dog during the perioperative period is critical for a successful outcome after adrenalectomy. (See Suggested Readings for more information on the perioperative and surgical management of dogs with a pheochromocytoma.)

Long-term medical management is designed to control excessive catecholamine secretion. The α-adrenergic blocking drug phenoxybenzamine (0.50 mg/kg, administered

orally q12h initially) is used to prevent severe clinical manifestations of hypertension. Propranolol or atenolol may also be necessary to control tachycardia and cardiac arrhythmias. However, propranolol and atenolol should be given only after  $\alpha$ -adrenergic blockade has been initiated because severe hypertension may develop after blockade of  $\beta$ -receptormediated vasodilation in skeletal muscle.

#### **Prognosis**

The prognosis depends in part on the size of the adrenal mass, presence of metastasis or local invasion of the tumor into adjacent blood vessels or organs (e.g., kidney), avoidance of perioperative complications if adrenalectomy is performed (i.e., hypertension, cardiac arrhythmias, respiratory distress, and hemorrhage), and the presence and nature of concurrent disease. Surgically excisable tumors carry a guarded to good prognosis. Survival time in our dogs that underwent adrenalectomy and survived the immediate postoperative period ranged from 2 months to longer than 3 years. If metastatic disease is not present, perioperative complications are prevented, and serious concurrent disease not present, the dog has the potential to live a significant length of time (i.e., more than a year). Pretreatment with an αadrenergic blocking drug before surgery and the involvement of an experienced anesthesiologist and surgeon with expertise in adrenal surgery help minimize potentially serious perioperative complications associated with anesthesia and digital manipulation of the tumor. Medically treated dogs can live longer than 1 year from the time of diagnosis if the tumor is relatively small (less than 3 cm diameter), vascular invasion is not present, and treatment with an α-adrenergic blocking drug is effective in minimizing the deleterious effects of episodic excessive catecholamine secretion by the tumor. Most dogs die or are euthanized because of complications caused by excessive catecholamine secretion, complications caused by tumor-induced venous thrombosis, or complications caused by invasion of the tumor or its metastases into surrounding organs.

#### INCIDENTAL ADRENAL MASS

Ultrasonography has become a routine diagnostic tool for the evaluation of soft tissue structures in the abdominal cavity. One consequence of abdominal ultrasonography is the unexpected finding of a seemingly incidental adrenal mass. Many factors determine the aggressiveness of the diagnostic and therapeutic approach to an adrenal mass, including the severity of concurrent problems, the original reason for performing abdominal ultrasound, the age of the dog or cat, the likelihood that the mass is hormonally active, the likelihood that the mass is a malignant or benign tumor, the size and invasiveness of the mass, and the client's desires and willingness to pursue the problem. The first consideration is to be certain that an adrenal mass exists. Abdominal ultrasound should always be repeated to confirm that the mass is

a repeatable finding. An adrenal mass is suspected when the maximum width of the adrenal gland exceeds 1.5 cm, there is loss of the typical kidney-bean shape of the gland, and there is asymmetry in shape and size between the affected adrenal gland and the contralateral adrenal gland. Bulbous enlargement of the cranial or caudal pole of the adrenal gland is common in dogs with normal adrenal glands and can be misinterpreted as an adrenal mass.

An adrenal mass is not always neoplastic or producing and secreting a hormone. The mass may be normal tissue, granuloma, cyst, hemorrhage, or an inflammatory nodule. Adrenalectomy is the treatment of choice if the mass is malignant and has not spread, but adrenalectomy may not be indicated if the mass is benign, small, hormonally inactive, and not invading surrounding structures. Unfortunately, it is not easy to determine whether an adrenal mass is neoplastic and malignant or benign before surgical removal and histopathologic evaluation. Guidelines to suggest malignancy include size of the mass, invasion of the mass into surrounding organs and blood vessels, and identification of additional mass lesions with abdominal ultrasound and thoracic radiographs. The bigger the mass, the more likely it is to be malignant and the more likely metastasis has occurred, regardless of findings on abdominal ultrasound and thoracic radiographs. Cytologic evaluation of specimens obtained by ultrasound-guided fine-needle aspiration of the adrenal mass may provide guidance regarding malignancy and origin of the mass (i.e., adrenal cortex versus medulla).

An adrenal tumor may secrete a hormone or be nonfunctional. Excess secretion of cortisol, catecholamines, aldosterone, progesterone, and steroid hormone precursors have been documented in dogs and cats (see Table 53-7). The most common functional adrenal tumors secrete cortisol or catecholamines. Aldosterone-secreting adrenal tumors causing primary hyperaldosteronism (Conn's syndrome) are uncommon in dogs and cats. Excessive secretion of aldosterone causes sodium retention and potassium depletion, which is manifested as increased serum sodium (greater than 155 mEq/L) and decreased serum potassium (less than 3.0 mEq/L) concentrations. Hypokalemia causes lethargy and weakness, which are the most common clinical signs of primary hyperaldosteronism. Hypernatremia causes systemic hypertension. An adrenal mass should be identified on abdominal ultrasound, and the contralateral adrenal gland should be normal in size and shape. Documenting an increased baseline plasma aldosterone concentration is used to confirm the diagnosis.

Adrenal tumors secreting progesterone, 17-hydroxyprogesterone (see the section on atypical Cushing's syndrome, p. 830), and other adrenocortical steroid precursors have also been documented in dogs and cats. Progesterone-secreting adrenal tumors are identified most commonly in cats. Excessive progesterone secretion in affected cats caused diabetes mellitus and feline fragile skin syndrome, characterized by progressively worsening dermal and epidermal atrophy, patchy endocrine alopecia, and easily torn skin (see Fig. 53-20). Clinical features mimicked feline hyperadrenocorticism, which is the primary differential diagnosis. Results of tests of the pituitary-adrenocortical axis are normal to suppressed in cats with progesterone-secreting adrenal tumors, and the contralateral adrenal gland is normal in size and shape on abdominal ultrasound. Diagnosis requires documenting an increased plasma progesterone concentration.

After discovering an incidental mass, the clinician should review the history, physical examination, and results of routine blood and urine tests for evidence of hyperadrenocorticism, hyperaldosteronism, or pheochromocytoma and should perform the appropriate tests to confirm the diagnosis. Whenever surgical removal of an adrenal mass is planned, a UCCR and an LDDS test should be evaluated and the perioperative management adjusted accordingly if test results are consistent with hyperadrenocorticism. If hormonal tests for hyperadrenocorticism are normal and clinical signs suggestive of pheochromocytoma are present, the clinician should assume that the adrenal mass is a pheochromocytoma and treat with an α-adrenergic antagonist before adrenalectomy (see p. 843). If the diagnostic evaluation does not support hyperadrenocorticism or pheochromocytoma, the anesthesiologist should be prepared to manage intraoperative blood pressure and cardiac rhythm disturbances should the mass turn out to be a pheochromocytoma.

An aggressive diagnostic and therapeutic approach is often not warranted for a small adrenal mass (less than 2 cm in maximum width), especially if the dog or cat is healthy and there are no clinical signs related to adrenal dysfunction. In these cases, it may be preferable to determine the rate of growth of the mass by repeating abdominal ultrasound initially at 2, 4, and 6 months. If the adrenal mass has not changed in size during this time, the clinician can increase the time interval between ultrasound evaluations to every 4 to 6 months (Fig. 53-21). However, if the adrenal mass is increasing in size and/or clinical signs develop, the clinician should consider adrenalectomy.

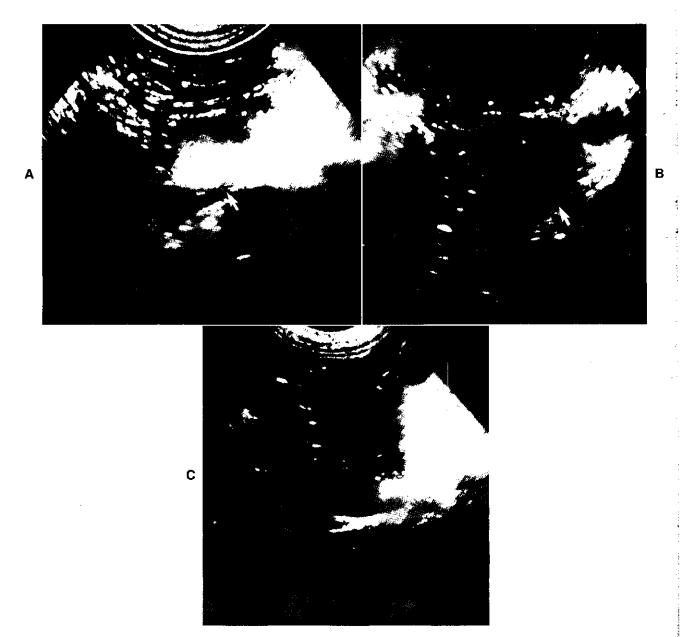


FIG 53-21

**A,** An 11-year-old male castrated Doberman Pinscher mix presented for clinical signs consistent with acute gastroenteritis. Abdominal ultrasound identified a 1.4-cm diameter adrenal mass (arrow) and a normal-size contralateral adrenal gland. The history, physical examination, and results of routine blood and urine tests were not supportive of adrenal disease, and the dog responded to symptomatic therapy for acute gastroenteritis. The adrenal mass was periodically evaluated with ultrasound. Over the ensuing 2 years the dog remained healthy and there was minimal growth or change in the echogenicity of the adrenal mass. **B,** The adrenal mass 1 year after presentation; maximum diameter was 1.8 cm. **C,** The adrenal mass 2 years after presentation; maximum diameter was 2.0 cm.

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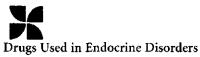
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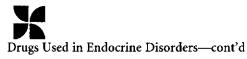
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GENERIC NAME (TRADE		RECOMMENDED DOSE				
NAME)	PURPOSE	DOG	CAT			
Aminoglutethimide (Cytadren)	Treat feline hyperadrenocorticism	Not applicable	30 mg/cat PO q12h			
Calcium-injectable and oral preps	Treat hypocalcemia, hypoparathyroidism	See Box 55-7	See Box 55-7			
Carbimazole (Neo- Mercazole)	Treat feline hyperthyroidism	Not applicable	5 mg PO q12h initially; increase q 2 weeks to effect			
Chlorpropamide (Diabinase)	Treat partial central diabetes insipidus	5-20 mg/kg PO q12h	Unknown			
Chlorothiazide (Diuril)	Treat central/renal diabetes insipidus	20-40 mg/kg PO q12h	20-40 mg/kg PO q12h			
Desmopressin (DDAVP)	Treat central diabetes insipidus	1-4 drops of nasal spray in eye q12-24h; 0.1 mg tablet PO q8-12h	1-4 drops of nasal spray in eye q12-24h; 0.05 mg tablet PO q8-12h			
Desoxycorticosterone pivalate (DOCP)	Treat hypoadrenocorticism	2.2 mg/kg IM or SC q25 days	2.2 mg/kg IM or SC q 25 days			
Dexamethasone sodium phosphate	Treat acute Addisonian crisis	0.5-1.0 mg/kg IV, repeat q12h at 0.05 to 0.1 mg/kg in IV fluids	0.5-1.0 mg/kg IV, repeat q12h at 0.05-0.1 mg/kg in IV fluids			
Diazoxide (Proglycem)	Supportive treatment for β cell tumor	5 mg/kg PO q12h initially; increase as needed	Unknown			
Diethylstilbesterol	Treat estrogen-responsive dermatosis of spayed female dogs	0.1-1.0 mg PO q24h 3 weeks per month; once respond, 0.1- 1 mg q4-7 days	Not applicable			
Doxorubicin (Adriamycin)	Treat canine thyroid neoplasia	30 mg/m² BSA IV q3-6 weeks	Not applicable			
Fludrocortisone acetate (Florinef)	Treat hypoadrenocorticism	0.01 mg/kg PO q12h initially	0.05-0.1 mg/cat PO q12h			
Glipizide (Glucotrol) Glucagon USP	Treat feline type 2 diabetes Treat hypoglycemia caused by β cell neoplasia	Not applicable 5-10 ng/kg/min as continuous IV infusion; adjust dose to effect	2.5-5 mg/cat PO q12h Unknown			
Glyburide (Diabeta, Micronase)	Treat feline type 2 diabetes	Not applicable	0.625-1.25 mg/cat PO q24h			
Growth Hormone-porcine origin	Treat GH-responsive dermatosis Treat pituitary dwarfism	0.1-0.3 IU/kg SC 3 times/week for 4 to 6 wks	Unknown			
Hydrocortisone hemisuccinate	Treat acute addisonian crisis	2-4 mg/kg IV, then administer dexamethasone in IV fluids	2-4 mg/kg IV, then administer dexamethasone in IV fluids			
Hydrocortisone phosphate	Treat acute crisis	2-4 mg/kg IV, then administer dexamethasone in IV fluids	2-4 mg/kg IV, then administer dexamethasone in IV fluids			
Insulin	Treat diabetic ketoacidosis Treat diabetes mellitus Supportive treatment for hyperkalemia	See Box 52-9 See Table 52-2 See Table 55-3	See Box 52-9 See Table 52-2 See Table 55-3			
Ketoconazole (Nizoral)	Treat hyperadrenocorticism	5 mg/kg PO q12h initially; increase to effect q 2 weeks	Not recommended			
Medroxyprogesterone acetate	Treat pituitary dwarfism	2.5-5.0 mg/kg SC q 3 weeks initially	Not applicable			
Megestrol acetate (Ovaban)	Treat feline endocrine alopecia	Not applicable	2.5-5 mg/cat PO q48h; once respond, then q7-14 days			



GENERIC NAME (TRADE	elevente militaria en el Cantillo de la Cantillo de la Cantillo de la Cantillo de Cantillo	RECOMMEN	DED DOSE
NAME)	PURPOSE	DOG	CAT
Melatonin	Treat congenital adrenal hyperplasia-like syndrome, Alopecia-X	3-6 mg PO q12-24h	Not applicable
Methimazole (Tapazole)	Treat hyperthyroidism	<ol> <li>2.5 mg/dog PO q12h initially; increase q2 weeks to effect</li> </ol>	2.5 mg/cat PO q12h initially; increase q2 weeks to effect
Methyltestosterone	Treat testosterone- responsive dermatosis	1 mg/kg (max, 30 mg) PO q48h; once dog responds, then q4-7 days	Not applicable
o,p'DDD (Mitotane, Lysodren)	Treat canine hyperadrenocorticism	Induction: 25 mg/kg PO q12h until controlled Maintenance: 25-50 mg/kg PO per week initially	Not recommended
Phenoxybenzamine (Dibenzyline)	Supportive treatment for pheochromocytoma	0.5 mg/kg PO q12h initially	Unknown
Prednisolone sodium succinate	Treat acute addisonian crisis	4-20 mg/kg IV, then administer dexamethasone in IV fluids	4-20 mg/kg IV, then administer dexamethasone in IV fluids
Prednisone (dogs), prednisolone (cats)	Chronic treatment of hypoadrenocorticism	0.25 mg/kg PO q12h initially	2.5-5.0 mg/cat PO q12-24h initially
,	Supportive treatment for β cell tumor	0.25 mg/kg PO q12h initially; increase as needed	2.5 mg/cat PO q12h initially; increase as needed
Prednisolone sodium succinate (Solu-Delta- Cortef)	Treat acute addisonian crisis	4-20 mg/kg IV, then administer dexamethasone in IV fluids	4-20 mg/kg IV, then administer dexamethasone in IV fluids
Sodium levothyroxine- synthetic T4	Treat hypothyroidism	0.02 mg/kg PO q12h initially, unless formulated for q24h	0.05-0.1 mg/cat PO q12- 24h initially
Somatostatin (Octreotide)	Supportive treatment for $\beta$ cell tumor	10-40 μg/dog SC q8-12h	Unknown
Streptozotocin	Treat canine β cell tumor	500 mg/m <sup>2</sup> BSA IV during 0.9% saline diuresis q 3 weeks; see Box 52-12	Not applicable
Trilostane (Vetoryl)	Treat hyperadrenocorticism	1-2 mg/kg q 12h initially; adjust to effect	1-2 mg/kg q24h initially; adjust to effect
Vitamin D preparations	Treat hypoparathyroidism	See Box 55-7	See Box 55-7

PO, By mouth; IM, intramuscular; SC, subcutaneous; BSA, body surface area; GH, growth hormone; IV, intravenous.

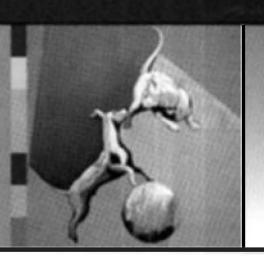
# PART SEVEN

# METABOLIC AND ELECTROLYTE DISORDERS

Richard W. Nelson, Sean J. Delaney and Denise A. Elliott

# CHAPTER

## Disorders of Metabolism



#### CHAPTER OUTLINE

POLYPHAGIA WITH WEIGHT LOSS OBESITY HYPERLIPIDEMIA

#### POLYPHAGIA WITH WEIGHT LOSS

In most dogs and cats polyphagia is usually accompanied by weight gain, and weight loss is accompanied by partial or complete anorexia. In some, however, polyphagia with concurrent weight loss is the presenting complaint. The most common cause of polyphagia with concurrent weight loss is inadequate caloric intake (Table 54-1). Daily caloric needs may not be met if inadequate quantities of food are being fed or if the diet is not complete and balanced or is of poor quality. Alternatively, the client may not recognize changes in nutritional needs (e.g., during pregnancy and lactation and at times of strenuous exercise, such as during hunting season) and may continue to feed the animal at previously adequate caloric levels.

Endocrinopathies and gastrointestinal tract disorders also cause polyphagia and weight loss in some dogs and cats (see Table 54-1) as a result of an increase in basal metabolism (hyperthyroidism), inadequate assimilation of dietary nutrients (gastrointestinal tract disorders), or inappropriate use of nutrients (diabetes mellitus). Gastrointestinal tract disorders include parasitism, pancreatic exocrine insufficiency, infiltrative bowel disorders, lymphangiectasia, and neoplasia (most notably lymphoma). In most of these disorders the history and physical findings usually provide valuable clues to the diagnosis. For example, polyuria and polydipsia are common signs in diabetes mellitus. A thyroid nodule is usually palpable in dogs and cats with hyperthyroidism.

Bulky, voluminous stools are noted in animals with pancreatic exocrine insufficiency. Diarrhea and vomiting may occur in animals with gastrointestinal tract disorders, and palpation of the abdomen may reveal abnormal loops of intestine and mesenteric lymphadenopathy. The last condition may be discernible in animals with any of the infiltrative diseases but is especially noticeable in those with gastrointestinal tract lymphoma, eosinophilic enteritis, or histoplasmosis.

In addition to routine questions posed to the client, the clinician should assess the type of foods offered, daily caloric intake, feeding routines, and competition for food from other dogs or cats. Daily caloric requirements in cats and dogs are quite variable and depend on numerous factors, such as signalment and the amount of daily physical activity. The average daily caloric intake can be calculated using the equation for the resting energy requirement (RER): 70× body weight in kilograms raised to the power. This can be calculated on a simple calculator with a square root button. The body weight in kilograms is multiplied by itself three times, and the square root of the result is taken twice before multiplying by 70. This value for RER has a unit of kcal per day and is multiplied by a factor to derive the maintenance energy requirement (MER). The factor for a neutered cat is 1.2, an intact cat's factor is 1.4, a neutered dog's factor is 1.6, and an intact dog's is 1.8. The daily caloric requirements in any individual dog or cat may vary by as much as 50% more or less than this calculation. Although this represents a large range for normal caloric intakes, the clinician may have a greater suspicion that an inadequate amount of calories is being fed if the amount based on the diet history is closer to 50% of MER. At the same time, consumption of calories closer to 150% of MER may increase the suspicion that adequate calories are being fed but that an endocrinopathy and/or gastrointestinal tract disorder may be leading to polyphagia with concurrent weight loss. If the results of comparing the caloric intake to the calculated MER prove equivocal



Differential Diagnosis for Polyphagia and Weight Loss

#### **ETIOLOGY**

Inadequate nutrition Hyperthyroidism Diabetes mellitus Gastrointestinal disease **Parasitism** Infiltrative bowel disease: plasmacytic, lymphocytic, eosinophilic, lymphoma Histoplasmosis Lymphangiectasia Pancreatic exocrine insufficiency

Protein-losing nephropathy

Hypothalamic mass

#### **DEFINITIVE DIAGNOSTIC TESTS**

Response to diet change Serum T<sub>4</sub> and free T<sub>4</sub> concentrations Blood glucose concentration and urinalysis

Fecal examination, trial therapy Intestinal biopsy

Intestinal biopsy, serology Intestinal biopsy

Serum trypsin-like immunoreactivity, response to therapy Urinalysis, urine protein/creatinine ratio

Computed tomography, magnetic resonance imaging

or cannot be attained, simply feeding more food or calories and reassessing the patient's weight may be illuminative.

A complete blood count, serum biochemistry panel, measurement of baseline thyroxine concentration, urinalysis, and fecal examination for parasites should be done if the history and physical findings are unremarkable. Results of these tests usually help identify additional specific diagnostic tests that may be required to establish a definitive diagnosis (see Table 54-1). Inadequate nutrition should be suspected if the initial blood test results are unremarkable. Changes in the type of foods provided, daily caloric intake, and feeding routine should be made to ensure that the animal has an adequate caloric intake of a palatable and nutritionally complete and balanced food. The animal's body weight should be determined 2 and 4 weeks after the start of an appropriate diet. The resolution of signs and weight gain confirm the diagnosis. Failure to gain weight indicates problems with client compliance or the presence of occult disease, most likely disease involving the gastrointestinal tract.

#### OBESITY

Obesity is a clinical syndrome that involves the excess accumulation of body fat. Obesity is considered the most common form of malnutrition in small animal practice. Indeed, surveys suggest that 25% to 40% of cats and dogs presented to veterinary clinics are overweight or obese. The significance of obesity pertains to its role in the pathogenesis of a variety of diseases and its ability to exacerbate preexisting disease and decrease lifespan. Obesity has been associated with an increased incidence of arthritis, diabetes mellitus, hepatic lipidosis, feline lower urinary tract disease (FLUTD), urine incontinence in spayed bitches, constipation, dermatitis, cardiovascular problems, respiratory problems, and increased anesthetic and surgical risk (Box 54-1). In addition, Scarlett et al. (1998) found a threefold increase in risk of death in



BOX 54-1

Potential Adverse Effects of Obesity

Decreased lifespan

Problems with ambulation-aggravation of joint disease, intervertebral disk disease

Problems with respiration—impaired lung compliance, Pickwickian syndrome

Cardiovascular disease and systemic hypertension Exercise intolerance

Carbohydrate intolerance—predisposition for diabetes mellitus

Hyperlipidemia

Hepatic lipidosis

Predisposition for pancreatitis

Problems with constipation

Predisposition for feline lower urinary tract disease

Predisposition for urinary incontinence in spayed female dogs

Predisposition for reproductive problems—dystocia

Predisposition for dermatologic problems—seborrhea, pyoderma

Increased surgical and anesthetic risk

Increased susceptibility to infectious diseases (?)

obese middle-aged cats compared with the risk in lean middle-aged cats. In dogs Kealy et al. (2002) found that dogs that were kept lean throughout their life lived almost 2 years longer than control-group littermates that were overweight. The lean dogs also did not need treatment for co-morbidities such as osteoarthritis until later in life.

Obesity develops when energy intake consistently exceeds daily energy expenditure. Numerous environmental and social factors contribute to the development of obesity



#### Causes of Obesity in Cats and Dogs

#### **Primary Obesity**

Excess caloric intake
Energy dense food
Inappropriate feeding practices
Inadequate feeding guidelines
Ad libitum feeding
Reduced energy expenditure
Genetic predisposition
Obese client

#### Secondary Obesity

Hypothyroidism
Hyperadrenocorticism
Hyperinsulinism
Acromegaly
Hypopituitarism
Hypothalamic dysfunction
Drugs
Glucocorticoids
Progestagens
Phenobarbital
Primidone

(Box 54-2). These include decreased daily exercise as a result of confinement to the house and overfeeding of the pet. Clients may overfeed their pet because a good appetite is perceived as a sign of good health, they may use food as a palliative agent when they leave the pet on its own, they may replace exercise with food, and they often indulge begging behavior because they find it endearing. Clients also tend to feed the same volume of food each day despite changes in energy requirements and the energy density of foods provided. Daily energy requirements vary according to the environmental temperature, the life stage of the pet (i.e., growth, pregnancy, lactation, adult maintenance, old age), the neuter status, and the activity level of the pet. Therefore it is necessary to adjust the amount of food according to these factors. Feeding errors also arise when a client purchases a different type of food with a higher energy density but does not reduce the amount accordingly. It is worth noting that dry extruded foods can now range from 200 kcal per 8-ounce cup to over 600 kcal per cup. Overfeeding may also arise if the feeding guidelines provided by pet food manufacturers are incorrect. In some situations clients are simply not aware that they are overfeeding their pet. Ad libitum feeding may also predispose to overeating, particularly if the pet is bored and inactive. Likewise, highly palatable foods encourage overconsumption. Snacks and treats are a significant silent contributor to excess daily caloric intake as well. It takes only about 11 extra calories a day for a pet to gain I pound over the course of a year; many common treats provide between 50 and 100 extra calories apiece.

Obese clients may be more likely to have obese pets. The client's sedentary lifestyle may contribute to a lack of exercise by the pet, and the consumption of high-fat foods by the client may increase the likelihood that these energy-dense scraps are fed to the pet. In addition, it is possible that obese clients do not believe (or recognize) that obesity is a major problem for their pet.

Because of genetic differences, some animals have significantly lower energy requirements and therefore require fewer calories per day to maintain their ideal body weight. These genetic differences may be reflected by the increased propensity of certain dog breeds to gain weight. Breeds commonly recognized as at risk for obesity include the Labrador Retriever, Golden Retriever, Cocker Spaniel, Collie, Dachshund, Cairn Terrier, Shetland Sheepdog, Beagle, Cavalier King Charles Spaniel, and Basset Hound. Neutering has been associated with an increased risk of obesity. It has been suggested that hormonal alterations secondary to neutering may alter energy expenditure and the regulation of food intake. Obesity has been reported to be more common in female neutered dogs and male neutered cats.

Obesity is less likely to result from a disease process or drug. Indeed, it has been suggested that less than 5% of obesity is due to a disease or drug. Endocrine abnormalities associated with obesity include hypothyroidism, hyperadrenocorticism, hyperinsulinism, and acromegaly. Drugs such as progestagens and corticosteroids have been associated with the development of obesity.

#### Diagnosis

Obesity is defined as a "pathological condition characterized by an accumulation of fat much in excess of that required for optimal body function" (Mayer, 1973). However, what is an excess amount of body fat, and what is an acceptable amount? To answer these questions, the clinician must accurately determine the amount of body fat. Body fat can be assessed by techniques such as morphometric measurements, dilutional methods, bioelectrical impedance analysis, dual energy X-ray absorptiometry, densitometry, computed tomography, magnetic resonance imaging, determination of total body electrical conductivity, determination of total body potassium, and neutron activation analysis. Although numerous methods exist to determine body fat, measurement of body weight, calculation of a body condition score (BCS), and morphometric measurements remain the most clinically useful techniques in small animal practice.

Measurement of body weight is the simplest technique available and should be included in the examination of every animal. Body weight provides a rough measure of total body energy stores, and changes in weight reflect energy and protein balance.

Body condition scoring provides a quick and simple subjective assessment of the animal's body condition. The two most commonly used scoring systems in small animal practice are a 5-point system in which a BCS of 3 is considered ideal and a 9-point system in which a BCS of 5 is considered ideal. Larger numbers are used for patients with greater

adiposity. Each point above and below 5 on the 9-point system has been validated to correspond with an increase or decrease in adiposity or weight of 10% to 15%. Thus a patient that has a BCS of 7 out of 9 is 20% to 30% overweight as a result of the accumulation of adipose tissue. Likewise, pets can be classified as being thin, lean, of optimal weight, overweight, or obese (Box 54-3). The BCS technique depends on operator interpretation and does not provide any precise quantitative information concerning alteration in fat-free or lean body mass relative to fat mass.

Height and circumferential measurements of the abdomen, hip, thigh, and upper arm are commonly used to estimate the percentage of body fat in humans. Circumferential measurements have also been developed to estimate the percentage of body fat in cats. The Feline Body Mass Index (FBMI) is determined by measuring the rib cage circumference at the level of the ninth cranial rib and deter-



A

BOX 54-3

Body Condition Scoring (BCS) System for Cats and Dogs Using a 5-Point System

Thin (BCS 1/5) Underweight; no obvious body fat Lean (BCS 2/5) Skeletal structure visible; little body fat Optimal Rib cage easily palpable but not (BSC 3/5) showing; moderate amount of body fat Overweight Rib cage barely palpable; body (BCS 4/5) weight more than normal Obese (BCS 5/5) Rib cage not palpable; large amount of body fat; physical impairment resulting from excess body fat

mining the leg index measurement (LIM), which is the distance from the patella to the calcanealtuber (Fig. 54-1, A and B). The percentage of body fat can be calculated as 1.5 to 9 (rib cage measurement minus LIM) or determined by consulting a reference chart (Fig. 54-2). Cats with more than 30% body fat are candidates for a weight loss program. The FBMI is a very simple yet objective tool for determining the body fat content of the cat. In addition, it is particularly valuable in persuading clients that their cat is indeed overweight and in need of weight loss. Pelvic circumference in relation to the distance from hock to stifle has been shown to predict body fat in dogs. Whether morphometric measurements or BCS is used, providing a quantitative assessment of a patient's degree of adiposity can be helpful in diagnosing obesity, which is typically defined as being approximately 25% over one's ideal body weight.

#### **Treatment**

After determining that a patient is overweight or obese, the clinician should obtain a thorough dietary history to calculate the patient's daily caloric intake. The clinician should gather the following information:

- The name, manufacturer, and type (i.e., pouched versus canned versus dry) of the current food(s)
- The amount of food that is fed each day (pouches, cans, cups, or grams of food)
- The method of feeding (ad libitum versus meal fed)
- The person responsible for feeding the patient
- Additional persons who may feed the patient (especially children, elderly parents, or friendly neighbors)
- The number and type of snacks or human foods given each day
- The potential access to foods for other pets





**FIG 54-1 A,** Length of the lower leg (LIM) from the middle of the patella. **B,** Measurement of the rib cage circumference.

В

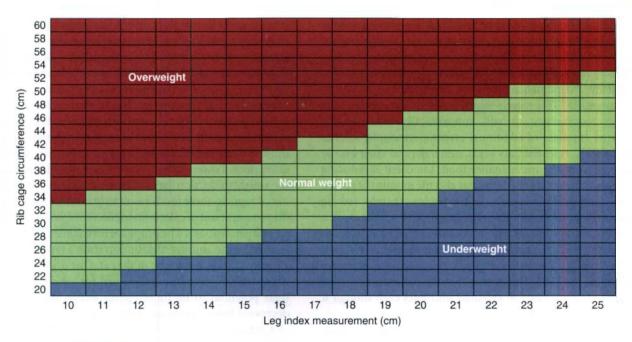


FIG 54-2 Feline body mass index (FBMI).

The patient's current body weight should be recorded and a BCS assigned. The BCS can be used to determine the percentage of body weight that must be lost. Remembering that each point above a 5 on a 9-point scale represents an additional 10% to 15% of weight over ideal, the clinician can calculate the percentage of weight that should be lost. For example, a patient that has a BCS of 8 out of 9 is 30% to 45% overweight. For reasons that will be discussed later, patients should not lose more than 2% of their body weight per week. Therefore it should be expected that most overweight and obese patients will take at least several months to lose enough adipose tissue to attain their ideal body weight. Given the necessary length of time, it is imperative to break down the ultimate goal of an ideal body weight into smaller goals that can be achieved in shorter periods of time. Therefore the clinician may recommend that the patient lose 2% to 4% of body weight every 2 weeks; later, monthly goals of 4% to 8% may be set. These shorter-term goals are typically more manageable and provide more opportunities for adjustment of a weight loss plan if needed and for praise if the plan is proving effective.

A rate of weight loss of 1% to 2% of current body weight per week is typically recommended for several reasons. First, greater rates of weight loss will require that the patient receive a very small allowance of food, which is most likely to encourage begging behavior and garbage scavenging. These undesirable behaviors, along with the small volume of food to be provided, can jeopardize client compliance. Second, weight loss greater than 2% of body weight per week is considered unhealthy and has been associated with a greater loss of lean body mass compared with fat mass. Third, rapid weight loss is most likely to result in a rebound weight gain effect after cessation of the program.

Given the large variation in energy requirement that can be seen in cats and dogs, the best method to determine the amount of calories to feed a patient to induce weight loss is the use of an accurate diet history. Typically, the weight of overweight and obese patients is relatively stable at presentation; therefore feeding 80% of the patient's current caloric intake based on an accurate diet history results in weight loss of 0.5% to 2% of body weight loss per week. In patients in which an accurate diet history cannot be determined or that are not roughly weight stable, the client may feed 80% of RER for cats and RER for dogs. Regardless of the method used to determine the number of calories to feed to initiate weight loss, clients should be told to expect to adjust the amount of food on the basis of frequent weigh-ins. Initially, it can be expected that some patients will gain weight on the new weight loss plan, some may stay weight stable, some may lose the desired amount, and some may even lose weight too quickly.

After determining the daily amount of calories to feed the patient, the clinician should consider the most suitable type of food. There are essentially two main dietary options: either feed a reduced amount of the regular maintenance food or feed a food that has been specifically formulated for weight reduction. It is not advisable to feed less of the regular food because this most likely was the food that resulted in the problem in the first place. More important, feeding a maintenance food decreases compliance and increases the risk of nutrient deficiency and unhealthy weight loss. Most foods designed for weight reduction are one-half to two-thirds less energy dense than typical maintenance foods. Therefore clients will not visually perceive as much of a decrease in "bowl fill" when feeding a food designed for weight reduction. Decreased energy density is achieved by

decreasing the fat content of the food, air-puffing kibble, increasing the moisture content of canned or pouched foods, and/or by adding fiber. There does appear to be some satiety effect by increasing "bowel fill". More significantly, canine and feline maintenance foods are formulated according to energy intake. This means that if a dog or cat eats its daily energy requirement, it will automatically consume the required amounts of additional essential nutrients, such as amino acids, essential fatty acids, minerals, and vitamins. By feeding less of the maintenance food, the client is reducing not only the amount of energy but also the amount of amino acids, fatty acids, minerals, and vitamins, thereby risking malnutrition, especially given the length of time that is often needed to achieve an ideal body condition. Conversely, foods that have been specifically formulated for weight reduction contain more essential nutrients relative to the energy content of the food. This means that the patient will receive the required amounts of essential nutrients even though it is ingesting fewer calories.

Foods formulated specifically for weight reduction typically vary according to energy density, fiber content, and caloric distribution (Tables 54-2 and 54-3). Most foods designed for weight reduction are less energy dense than maintenance foods. This enables a greater filling of both the bowl and the bowel, which should lead to increased compliance and satiety. Traditionally, higher-fiber foods are initially suggested for weight loss. Fiber is used as a bulking agent to decrease energy density and provide a satiating effect. However, there is conflicting research as to whether fiber increases satiety. Because some patients may not respond well to higher-fiber foods, some manufacturers do not use this nutritional strategy. Caloric distribution refers to the percentage of calories provided from protein, fat, and carbohydrate. Higher-protein foods have been reported to increase the proportion of fat loss while preserving or, indeed, increasing the lean body mass. The lean body mass is the most metabolically active portion of the body and includes skeletal muscle tissues. Preservation of lean body mass in humans has been shown to facilitate successful long-term maintenance of the ideal body weight once weight loss has been achieved. Lowering the percentage of calories from fat in foods helps reduce the energy density of the food because fat provides almost 2.5 times the amount of calories per gram as protein or carbohydrate does. Lower-carbohydrate foods specifically designed for weight reduction have become available. According to initial reports, these foods result in greater fat mass loss with the same amount of caloric restriction compared with highercarbohydrate foods. The proposed mechanism for this difference relates to shifting metabolism from a lypogenic state to a lypolytic state, especially in the cat. One drawback of some lower-carbohydrate foods designed for weight reduction is their potential to be more energy dense and thus have a decreased bowl- and bowel-filling effect.

Carnitine is an amino acid derivative that is vital for energy metabolism. Carnitine facilitates the movement of long-chain fatty acids across the mitochondrial membrane, where they are used for energy production. Carnitine supplementation is believed to facilitate weight loss by increasing the efficiency of "burning" fat as an energy source. However, a study evaluating the effect of carnitine supplementation on body weight loss failed to demonstrate any benefits (Center et al., 2000). Cats that received carnitine supplementation lost the same percentage of body weight in the same period of time as cats that did not receive carnitine supplementation. In addition, neither group of cats developed hepatic lipidosis.

As this chapter was being completed, a new drug (dirlotapide) has become available that helps reduce the appetites



**TABLE 54-2** Level of Key Nutrients in Selected Therapeutic Commercial Foods Suitable for Weight Loss in Dogs\*

	TYPE	PROTEIN (% ME)	FAT (% ME)	CHO (% ME)	FIBER (g/Mcal)	ME (kcal/can/cup)
Royal Canin Veterinary Diet Calorie Control CC High Protein	Dry	37.6	23.5	38.8	8.51	234/cup
Royal Canin Veterinary Diet Calorie Control CC High Protein	Can	42.6	53.1	4.2	6.29	263/12.7 oz can
Royal Canin Veterinary Diet Calorie Control CC High Fiber	Dry	34.4	28.1	37.5	23.64	232/cup
Purina Veterinary Diets OM Overweight Management	Dry	34.9	17.7	47.4	34.6	276/cup
Purina Veterinary Diets OM Overweight Management	Can	51.2	23.6	25.5	77.7	189/12.5 oz can
lams Veterinary Diets Restricted-Calorie	Can	31	39	30	5.36	445/14 oz can
Hill's Prescription Diet r/d	Dry	29. <i>7</i>	24.9	45.3	<i>7</i> 8	220/cup
Hill's Prescription Diet r/d	Can	29.7	24.6	<i>45.7</i>	<i>7</i> 1	296/14.25 oz can

ME, Metabolizable energy; CHO, carbohydrate.

<sup>\*</sup>Information obtained from manufacturers' published information. Foods with less than ~30% protein calories not listed.

晶

**TABLE 54-3** 

Level of Key Nutrients in Selected Therapeutic Commercial Foods Suitable for Weight Loss in Cats\*

	TYPE	PROTEIN (% ME)	FAT (% ME)	CHO (% ME)	FIBER (g/Mcal)	ME (kcal/pouch/ can/cup)
Royal Canin Veterinary Diet Calorie Control CC High Protein	Pouch	43.9	36	20.1	7.74	66/3 oz pouch
Royal Canin Veterinary Diet Calorie Control CC High Protein	Dry	44.4	23.4	32.1	11.2	235/cup
Royal Canin Veterinary Diet Calorie Control CC High Protein	Can	45.4	46.5	8.1	5.1	130/5.8 oz can
Royal Canin Veterinary Diet Calorie Control CC High Fiber	Dry	36.12	26.71	37.17	43	251/cup
Purina Veterinary Diets OM Overweight Management	Dry	56.2	20.5	23.3	17.6	321/cup
Purina Veterinary Diets OM Overweight Management	Can	43.1	34.4	22.4	26	150/5.5 oz can
lams Veterinary Diets Restricted-Calorie	Can	40	41	19	2.08	204/6 oz can
Hill's Prescription Diet r/d	Dry	40.4	24.9	34.7	41	263/cup
Hill's Prescription Diet r/d with Liver & Chicken	Can	41.3	24.5	34.2	50	114/5.5 oz can
Hill's Prescription Diet r/d	Can	38.2	25.2	36.5	55	116/5.5 oz can
Hill's Prescription Diet m/d	Dry	43	44.1	12.9	13	480/cup
Hill's Prescription Diet m/d	Can	45.7	40.7	13.6	15	156/5.5 oz can

ME, Metabolizable energy; CHO, carbohydrate.

of dogs in need of weight loss. According to the manufacturer's literature, dirlotapide is a selective microsomal triglyceride transfer protein inhibitor that blocks the assembly and release of lipoproteins into the bloodstream. The mechanism of action for producing weight loss is not completely understood, but it seems to result from reduced fat absorption and a satiety signal from lipid-filled enterocytes. Dirlotapide mainly acts locally in the gut to reduce appetite, increase fecal fat, and produce weight loss in the management of obesity in dogs. It appears that changes in long-term client feeding practices are important for prevention of weight regain after the use of this potentially promising new drug.

Once the daily caloric intake has been determined and the appropriate weight reduction food(s) chosen, the method of feeding should be determined. Ideally, the patient should receive meals rather than be fed ad libitum. The number of feedings per day can be selected to suit the client's schedule, but two to four meals per day is adequate. One member of the household should be selected to feed the patient. This will reduce inadvertent overfeeding by additional family members. If treats are typically fed or are desired, the client should be instructed to limit the number of treats to less than 10% of the daily caloric intake. Ideally, low-calorie treats should be selected. Commercial treats are available, but fruits (excluding grapes or raisins) and/or vegetables (no garlic or onions and not in patients with calcium oxalate urolithiasis) can be good alternatives for dogs and even some cats. Baby carrots are an especially good vegetable treat for dogs and contain only 4 kcal each. A small amount of lean

meat, such as skinless chicken breast, can be a good alternative treat for cats. It is also important to modify the behavior of the client such that the patient should not be allowed in the kitchen or dining room during meal preparation or eating if this is typically a tempting time to respond to begging. In addition, the client should inform and enlist the support of family members and neighbors so that they do not unknowingly give the patient additional calories. In some cases it may be useful for the client to use a food diary to record the amount of food and snacks fed each day. For other clients this technique is often met with resistance and should not be considered.

Multicat households in which one cat is obese and the remainder are of normal body weight or are lean can present some management problems. Ideally, cats should be fed in separate rooms, but this is not always possible. If it is possible, most cats can consume their caloric needs if given at least 4 hours of access to their food daily. Thus the time that cats are separated can be minimized. Moreover, fat cats usually cannot jump very high. Therefore it may be useful to place the food for the lean, healthy cats on an elevated bench or counter that the healthy cats can reach but the obese cat cannot. Alternatively, a hole can be cut into a cardboard box that is large enough to allow the lean cats to enter but small enough to restrict the entry of the overweight or obese cat. The lean cats are then fed in the box.

In addition to reducing the daily caloric intake, every effort should be made to increase the pet's daily energy expenditure by encouraging exercise. Toys that the cat or dog

<sup>\*</sup>Information obtained from manufacturers' published information. Foods with less than ~35% protein calories not listed.

can chase and play with should be encouraged. Laser pointers are particularly useful for encouraging cats to play. Ideally, dogs should receive two 20-minute walks per day. Swimming is an equally effective exercise, particularly for dogs with osteoarthritis. Providing the client with written instructions for weight loss will typically improve both compliance and success. Photographing the patient before institution of the weight reduction program will help clients see the effect of the weight loss on their pet. Institution of reward boards or incentive programs will also increase compliance with the weight reduction program.

Patients on weight reduction programs should be reevaluated every 2 weeks initially. The body weight, BCS, and/or FBMI should be recorded. The dietary history should be reviewed. Ideally, cats should achieve no more than a 2% body weight loss per week. More rapid weight loss in cats increases the risk of hepatic lipidosis. Dogs should achieve a 1% to 2% body weight loss per week. If the rate of weight loss exceeds a 2% body weight loss per week, then the amount of calories fed to the patient should be increased by 10% to 20%. If the patient has not lost any weight, the dietary history should be reevaluated for a source of additional calories and compliance with the weight loss plan confirmed. If no such reasons are found, the daily caloric intake should be further reduced by 10% to 20%.

Once the ideal body condition of the patient has been achieved, the daily caloric intake can be adjusted to maintain an ideal body condition. The patient's regular food may be changed to one formulated for weight maintenance or a light food. The patient should be reevaluated every 2 to 3 months after weight loss to ensure that weight stability is maintained and that the patient is not gaining weight on its new diet regimen.

#### **Prevention**

Ideally, clinicians should focus more on obesity prevention than on treatment because treatment can be very challenging. Energy requirements significantly decrease when the animal has a gonadectomy. Therefore prevention should begin at the time that the pet is neutered. Clients should be counseled about the risk factors of obesity (e.g., male neutered cats, female neutered dogs, inactive and indoor lifestyle, inappropriate feeding practices, energy-dense foods) and the consequences of obesity (e.g., increased incidence of lower urinary tract disease, diabetes mellitus, arthritis, decreased life span). It is important that clients be instructed in both how to feed their pet and how to regularly determine the pet's body condition such that they can maintain the ideal body condition of their pet. Weight education should be reinforced at least annually during the health examination.

#### HYPERLIPIDEMIA

Hyperlipidemia is defined as an increased concentration of triglycerides (hypertriglyceridemia), cholesterol (hypercholesterolemia), or both in the blood. In the fasted state (>10

hours without food), hyperlipidemia is an abnormal finding that represents either accelerated production or delayed degradation of lipoproteins. The lipoproteins function as a carrier system to transport water-insoluble triglycerides and cholesterol through the aqueous environment of blood. Lipoproteins consist of a triglyceride and cholesterol ester core surrounded by a surface layer of cholesterol, phospholipid, and apolipoproteins. The apolipoproteins (A, B, C, and E) are responsible for the structure of the lipoprotein particle, the binding of the particle to cell surface receptors, and the activation of enzymes. There are four major classes of lipoproteins. Each class differs in its lipid and apoprotein content and physicochemical characteristics, including size, density, and electrophoretic mobility. Lipoproteins are categorized according to their buoyant density on ultracentrifugation as chylomicrons, very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), or high-density lipoproteins (HDLs). The buoyant density is inversely proportional to the triglyceride content such that the chylomicrons are composed largely of triglyceride, whereas HDLs have virtually no triglyceride content. The classification system is somewhat arbitrary, and it should be understood that there is significant structural and functional heterogeneity within the classes. In addition, the system is a dynamic one, with one class producing another during its metabolism. Chylomicrons and VLDLs are primarily involved in triglyceride metabolism, whereas HDLs and LDLs are primarily involved in cholesterol metabolism. Dogs and cats are more resistant to the development of atherosclerosis than humans because HDLs predominate in dogs and cats, as opposed to the LDLs that predominate in humans.

#### **Pathophysiology**

After digestion and absorption occur, dietary cholesterol and triglyceride are packaged by the enterocyte into chylomicron particles. The chylomicron particles are secreted into the mesenteric lymph, through which they ultimately reach the systemic circulation via the thoracic duct. As the chylomicrons pass through the adipose and muscle tissue, they are exposed to lipoprotein lipase, an enzyme that is present on the surface of the capillary endothelial cells. After activation by apoprotein C-II, lipoprotein lipase hydrolyzes the triglyceride from the core of the lipoprotein to free fatty acids and glycerol. The free fatty acids diffuse into the adjacent tissue and are either resynthesized into triglycerides and stored (adipocytes) or used for energy by the cell (myocytes and other cells). The activity of lipoprotein lipase is influenced by several factors, including heparin, insulin, glucagon, and thyroid hormone. Depletion of the triglyceride component of the chylomicron alters the surface such that the chylomicron is converted into a chylomicron remnant. The remnant particle is rapidly recognized by specific hepatic receptors and removed from the circulation. Within the hepatocyte the contents of the chylomicron remnant are degraded and utilized. Chylomicrons are present in plasma 30 minutes to 2 hours after consumption of a fat-containing meal, and hydrolysis is normally complete within 6 to 10 hours.

The liver transforms excess free fatty acids that are not directly oxidized for energy into triglycerides. The free fatty acids may originate from residual dietary triglyceride present in chylomicron remnant particles, from endogenous production secondary to surplus dietary carbohydrate, and from excessive endogenous mobilization of free fatty acids. Free fatty acids can be mobilized from adipose tissue by the activation of the intracellular enzyme hormone-sensitive lipase (HSL). HSL hydrolyzes stored triglycerides into free fatty acids and glycerol. Stimulators of HSL include epinephrine, norepinephrine, adrenocorticotropic hormone (ACTH), corticosteroids, growth hormone, and thyroid hormone. In addition, HSL is activated by insulin deficiency. Activation of HSL is a normal physiologic response to provide the body with energy during periods of fasting. In addition, HSL can be inappropriately activated in several pathologic conditions associated with an altered metabolic state.

The triglycerides produced by the hepatocyte are packaged into VLDL particles and subsequently secreted into the bloodstream. VLDL particles are produced continuously by the liver and, in the fasting state, are the main carriers of triglycerides. In addition, VLDL particles are used to export cholesterol from the liver and therefore contain a significant proportion of cholesterol. Analogous to chylomicron metabolism, endothelial lipoprotein lipase hydrolyzes the triglyceride portion of the VLDL particle into free fatty acids and glycerol. The free fatty acids can either be oxidized for energy or reconstituted into triglycerides and stored. Removal of the triglyceride core converts the VLDL particle into a remnant particle, which may be removed and catabolized by the liver. Alternatively, a second endothelial lipase, hepatic lipase, can further remove any residual triglyceride and convert the VLDL remnant particle into an LDL particle.

The LDL particle is a cholesterol and phospholipid—rich entity that functions to transport cholesterol to tissues, where it may be used for membrane synthesis or steroid hormone production. Ultimately, the LDL particle can bind to LDL receptors and is removed by the liver. In addition to VLDL particles, the liver also secretes nascent HDL particles into the circulation. HDL particles act to scavenge excess unesterified cholesterol from the cells and other lipoproteins and return it to the liver for excretion into bile. This process is often referred to as reverse cholesterol transport.

Hypertriglyceridemia can develop secondary to increased chylomicron production (excessive dietary intake of lipid), ineffective clearance of the chylomicron particle, increased VLDL production (excessive dietary intake of lipid and/or carbohydrate, excessive endogenous production or mobilization of lipids), and ineffective clearance of the VLDL particle. Hypercholesterolemia can arise from increased production of the LDL precursor particle (VLDL) or as a result of reduced clearance of the LDL or HDL particle.

#### Classification

Postprandial hyperlipidemia is the most common cause of hyperlipidemia in dogs and cats. It is a normal physiologic manifestation that is due to the production of triglyceride-



#### Causes of Hyperlipidemia in Dogs and Cats

#### Postprandial Hyperlipidemia Primary Hyperlipidemia

Idiopathic hyperlipoproteinemia (Miniature Schnauzers) Idiopathic hyperchylomicronemia (cat) Lipoprotein lipase deficiency (cat) Idiopathic hypercholesterolemia

#### Secondary Hyperlipidemia

Hypothyroidism
Diabetes mellitus
Hyperadrenocorticism
Pancreatitis
Cholestasis
Hepatic insufficiency
Nephrotic syndrome
Drug-induced hyperlipidemia
Glucocorticoids
Megestrol acetate (cat)

rich chylomicrons and usually resolves within 2 to 10 hours. Pathologic abnormalities in plasma lipids and lipoproteins may be of genetic or familial origin (primary) or arise as a consequence of disease (Box 54-4).

Primary hypertriglyceridemias include the idiopathic hyperlipidemia of Miniature Schnauzers and hyperchylomicronemia of cats. Idiopathic hyperlipidemia of Miniature Schnauzers is characterized by severe hypertriglyceridemia resulting from excessive VLDL particles with or without concurrent hyperchylomicronemia and by mild hypercholesterolemia. The exact mechanism and genetics have not been fully elucidated. Feline familial hyperlipidemia is characterized as a fasting hyperchylomicronemia with a slight increase in VLDL particles. The defect is due to the production of an inactive form of lipoprotein lipase. Idiopathic hyperchylomicronemia has also been observed in dogs. Similar to the situation with the cat, the disease in the dog is characterized by hypertriglyceridemia, hyperchylomicronemia, and normal serum cholesterol concentrations. Idiopathic hypercholesterolemia is rare but has been reported in Doberman Pinschers and Rottweilers. Lipid derangements consist of hypercholesterolemia caused by an increased serum LDL concentration. The etiology of this disorder is unknown.

Diseases associated with secondary hyperlipidemia include endocrine disorders (hypothyroidism, diabetes mellitus, hyperadrenocorticism), nephrotic syndrome, and pancreatitis. Hypothyroidism is the most common cause of hypercholesterolemia in the dog. Hyperlipidemia secondary to hypothyroidism can be attributed to both a decrease in lipid synthesis and degradation (lipid degradation is more severely affected). Decreased lipoprotein lipase activity contributes to the impaired removal of triglyceride-rich lipoproteins. In addition, thyroid hormone deficiency reduces the

biliary excretion of cholesterol. The resultant increase in intrahepatic cholesterol concentration downregulates the hepatic LDL receptor, which increases the concentration of the circulating LDL and HDL cholesterol–rich particles.

Insulin deficiency (diabetes mellitus) reduces the production of lipoprotein lipase, which contributes to decreased clearance of triglyceride-rich lipoproteins. Furthermore, insulin deficiency activates HSL, causing the release of large quantities of free fatty acids into the blood. These free fatty acids are ultimately converted by the liver into triglycerides, packaged into VLDL particles, and secreted back into the circulation. Therefore the hypertriglyceridemia seen with diabetes mellitus is attributed to both a reduction of lipoprotein lipase and increased production and decreased clearance of VLDL particles. Insulin deficiency increases the synthesis of cholesterol in the liver. The increased intrahepatic cholesterol concentration downregulates the hepatocyte LDL receptor, consequently reducing the clearance of circulating LDL and HDL particles, which in turn causes hypercholesterolemia.

The mechanism of hypertriglyceridemia associated with hyperadrenocorticism is probably due to stimulation of HSL with release of free fatty acids into the circulation. Similar to the situation with diabetes mellitus, excess free fatty acids are converted into VLDL particles. In addition, glucocorticoids inhibit lipoprotein lipase activity, thereby reducing the clearance of triglyceride-rich lipoproteins.

#### **Clinical Features**

Waxing-and-waning vomiting, diarrhea, and abdominal discomfort are the most common clinical presentations associated with hypertriglyceridemia (Table 54-4). Severe hypertriglyceridemia (levels exceeding 1000 mg/dl) has been associated with pancreatitis, lipemia retinalis, seizures, cutaneous xanthomas, peripheral nerve paralysis, and behavioral



**TABLE 54-4** 

Clinical Signs and Potential Consequences of Hypertriglyceridemia and Hypercholesterolemia

#### **CLINICAL SIGNS CONSEQUENCES** Seizures Hypertriglyceridemia **Blindness** Seizures Abdominal pain **Pancreatitis** Anorexia Lipid-laden aqueous humor: Vomiting uveitis, blindness Diarrhea Lipemia retinalis Behavioral changes Xanthomas Lipemia retinalis **Uveitis** Xanthoma formation Hypercholesterolemia Peripheral neuropathy Corneal arcus lipoides Horner's syndrome Lipemia retinalis Tibial nerve paralysis Atherosclerosis Radial nerve paralysis

changes. Cutaneous xanthomas, which represent lipid-laden macrophages and foam cells, are the most common manifestation of hypertriglyceridemia in the cat. Severe hypercholesterolemia has been associated with arcus lipoides corneae, lipemia retinalis, and atherosclerosis.

In addition to the clinical manifestations, hypertriglyceridemia may also interfere with the results of several routine biochemical tests (Table 54-5). The degree of interference depends on the specific assay used by the laboratory, the species (canine versus feline), and the severity of the hypertriglyceridemia. In addition, hyperlipidemia may also cause hemolysis, which in turn can interfere with the results of some biochemical assays. Alternatively, hyperbilirubinemia may cause the cholesterol concentration to be falsely lower. These potential alterations in biochemical data must be considered when interpreting results in animals with hyperlipidemia. Fortunately, many laboratories will attempt to clear the hypertriglyceridemia by ultracentrifugation before performing the biochemical assays.

#### Diagnosis

The presence of lipemic serum suggests that the animal is hypertriglyceridemic. Lactescence refers to the opaque and milklike appearance of serum samples that occurs when the elevation of the triglyceride level is sufficient. Animals with lactescent serum typically have triglyceride concentrations that exceed 1000 mg/dl. Conversely, animals that are purely hypercholesterolemic do not exhibit lipemic or lactescent serum because the cholesterol-rich LDL and HDL particles are too small to refract light. Blood samples to confirm hyperlipidemia should be obtained after a fast that lasts at least 12 hours. A serum sample rather than whole blood or plasma should be submitted for assessment. The sample can be refrigerated or frozen for several days without affecting the assays. When assessing the sample for hypertriglyceridemia, the technician should not clear the sample before determination of the triglyceride concentration. Clearing lipemic samples by centrifugation removes chylomicrons, which will artificially lower the triglyceride result. Reference intervals for serum triglyceride concentration are typically 50 to 150 mg/dl for the adult dog and 20 to 110 mg/dl for the adult cat. Reference intervals for serum cholesterol concentration are typically 125 to 300 mg/dl for the adult dog and 95 to 130 mg/dl for the adult cat.

The chylomicron test can be helpful to delineate whether the lipemia is predominantly a chylomicron or a VLDL defect. The test is performed by refrigerating a serum sample for 12 hours. Chylomicrons are less dense than the other particles and hence will float to the top of the sample to form an opaque cream layer over a clear infranatant of serum. If the hypertriglyceridemia is due to excess VLDL particles, the serum sample will remain turbid. Formation of a cream layer over a cloudy serum layer suggests both excess chylomicrons and VLDL particles.

Lipoprotein electrophoresis can be used to distinguish the lipoproteins, and ultracentrifugation can provide a quantitative measurement of each of the lipoprotein classes. However,



**TABLE 54-5** 

Effect of Lipemia on Clinical Chemistry Analytes in Canine and Feline Sera\*

FALSE INCREAS	SE IN VALUES	FALSE DECREASE IN VALUES		
CANINE SERA	FELINE SERA	CANINE SERA	FELINE SERA	
Total bilirubin Conjugated bilirubin Phosphorus Alkaline phosphatase† Glucose† Total protein‡ Lipase Alanine aminotransferase	Total bilirubin Conjugated bilirubin Phosphorus Alkaline phosphatase† Glucose† Total protein‡	Creatinine Total CO <sub>2</sub> Cholesterol Urea nitrogen	Creatinine Total CO <sub>2</sub> Alanine aminotransferase	

Adapted from Jacobs RM et al: Effects of bilirubinemia, hemolysis and lipemia on clinical chemistry analytes in bovine, canine, equine and feline sera, Can Vet J 33:605, 1992.

both of these procedures are time consuming and are not routinely available for clinical application. The activity of lipoprotein lipase can be assessed by the heparin release test. Serum samples for the determination of triglyceride concentrations (and, if possible, lipoprotein concentrations) are obtained before and 15 minutes after the intravenous administration of heparin (90 IU/kg body weight in dogs; 40 IU/kg body weight in cats). Heparin causes the release of lipoprotein lipase from the endothelium and stimulates the hydrolysis of triglycerides. A defect in lipoprotein lipase is suspected if there is no difference between the serum triglyceride concentrations before and after the administration of heparin.

#### **Treatment**

Before therapy is recommended, every attempt should be made to determine whether the hyperlipidemia is primary or secondary to an underlying disease process. Hyperlipidemia secondary to an underlying disorder will typically resolve or improve with correction of the metabolic disturbance. Therefore each animal requires a full history, physical examination, complete blood count, serum biochemistry panel and thyroxine concentrations, and urinalysis. The results of the initial diagnostic evaluation may indicate the need for additional diagnostic tests such as abdominal ultrasound, pancreatic lipase immunoreactivity assay, and evaluation of an ACTH stimulation test. A recommendation to treat hyperlipidemia involves a lifelong commitment by the client and therefore must not be undertaken lightly. In general, severe hypertriglyceridemia (levels exceeding 1000 mg/dl) mandates treatment. In this circumstance catabolic mechanisms can be assumed to be overwhelmed, and the triglyceride level is very sensitive to a small increase from the intestine or liver. The triglyceride levels must be decreased to prevent possible complications, including pancreatitis. In other situations the recommendations will be influenced by additional variables, including the underlying disease process.

A realistic goal of therapy is to reduce the triglyceride concentration to less than 400 mg/dl, even though such a level will still be above the reference interval.

Chylomicrons are produced from dietary fat. Therefore restriction of dietary fat is the cornerstone of therapy for hypertriglyceridemia. The dietary history should be reviewed, and the diet altered to one that contains less than 20% fat on an metabolizable energy (ME) basis for dogs (Table 54-6) or lower if the patient is already on a lower-fat diet. Nutritional management of hypertriglyceridemia in cats is more difficult because of the limited availability of lower-fat commercial therapeutic foods that have less than 24% fat on an ME basis (Table 54-7). Care should be taken when using over-the-counter foods that appear to be lower in fat. Because the proximate analysis that is reported on pet food labels requires only a minimum crude fat percentage to be reported, there is no guarantee that the fat content is not significantly higher. In contrast, therapeutic foods typically provide the average fat content in product guides, which should more accurately reflect the actual fat content of the food. Treats should be restricted to no more than 10% of the daily caloric intake and changed to low-fat commercial varieties. Fruit or brown rice crackers without seasoning are useful alternatives for dogs. In addition to the provision of a lower-fat diet, the absolute caloric intake should be evaluated. If the animal is overweight, caloric restriction is indicated and beneficial because it decreases the production of VLDL particles from excess dietary energy. The plasma triglyceride concentration should be reevaluated after 8 weeks of a lower-fat diet. If the reduction in triglyceride concentration is less than ideal, the dietary history should be reevaluated to ensure that there are no extra fat calories from treats, no access to other pet foods, and no additional family members or neighbors who are inadvertently providing the animal with dietary fat. In addition, the medical record should be reviewed to ensure the exclusion of underlying disorders that would contribute to

<sup>\*</sup>Analytes were measured using Coulter DACOS (Coulter Diagnostics, Hialeah, Fla).

<sup>†</sup>Interference occurs only at very high concentrations of lipid.

<sup>‡</sup>When measured using a refractometer.



TABLE 54-6

Level of Key Nutrients in Selected Therapeutic Commercial Foods Used for the Management of Canine Hypertriglyceridemia\*

	TYPE	FAT (% ME)	PROTEIN (% ME)	ME (kcal/can/cup)
Royal Canin Veterinary Diet Low Fat LF	Dry	15.6	25.5	222/cup
Royal Canin Veterinary Diet Low Fat LF	Can	15.3	31.6	442/13.6 oz can
Purina Veterinary Diets OM Overweight Management	Dry	1 <i>7.7</i>	34.9	276/cup
lams Veterinary Diets Restricted-Calorie	Dry	1 <i>7</i>	24	238/cup

ME, Metabolizable energy.

盟

**TABLE 54-7** 

Level of Key Nutrients in Selected Therapeutic Commercial Foods Used for the Management of Feline Hypertriglyceridemia\*

	TYPE	FAT (% ME)	PROTEIN (% ME)	ME (kcal/can/cup)
Royal Canin Veterinary Diet Calorie Control CC High Protein	Dry	23.4	44.4	235/cup
Royal Canin Veterinary Diet Weight Formula	Dry	21.8	42.4	260/cup
Purina Veterinary Diets OM Overweight  Management	Drý	20.5	56.2	321/cup
lams Veterinary Diets Restricted-Calorie	Dry	23	34	277/cup
Hill's Prescription Diet w/d	Drý	23.8	38.8	281/cup

<sup>\*</sup>Information obtained from manufacturers' published information. Foods with less than 24% fat calories are listed.

hypertriglyceridemia. If the lower-fat commercial foods are not sufficient to control the hypertriglyceridemia, then a complete and balanced fat-restricted (10% to 14% ME for dogs, 15% to 19% ME for cats) home-prepared recipe can be formulated specifically for the animal using online software (such as at balanceit.com) or through a veterinary nutritionist (see acvn.org). Diets rich in omega-3 fatty acids have been suggested to improve hypertriglyceridemia in humans by decreasing the production of VLDL particles. In addition, fish oils are poor substrates for triglyceridesynthesizing enzymes, and their use leads to the formation of triglyceride-poor VLDL particles. Some clinicians have recommended fish oil rich in long chain omega-3 fatty acids (i.e., EPA and DHA) in the amount of 200 to 220 mg/kg body weight/day to assist in the management of hypertriglyceridemia, especially in dogs refractory or incompletely responsive to dietary fat restriction.

Treatment with drugs, all of which have the potential for toxicity, should be undertaken with particular care. In general, drugs should not be used in animals whose scrum triglyceride concentration is less than 500 mg/dl. Several classes of drugs are used to treat hypertriglyceridemia in humans; however, there are few reports of their use in cats and dogs. Until there are further studies evaluating the dose, effect, and toxicity, drug therapy is indicated only in animals that have clinical signs associated with severe elevations in

triglyceride concentrations that cannot be ameliorated by dietary therapy, which is very uncommon in one of the author's (SJD) clinical experience.

Niacin (100 mg/day in dogs) reduces serum triglyceride concentrations by decreasing fatty acid release from adipocytes and reducing the production of VLDL particles. Adverse effects are frequent, mainly because of the associated release of the prostaglandin prostacyclin, and include vomiting, diarrhea, erythema, pruritus, and abnormalities in liver function tests. Fibric acid derivatives (clofibrate, bezafibrate, gemfibrozil, ciprofibrate, fenofibrate) lower plasma triglyceride concentrations by stimulating lipoprotein lipase activity, in addition to reducing the free fatty acid concentration, which decreases the substrate for VLDL synthesis. In humans the fibrates generally lower plasma triglyceride concentrations by 20% to 40%. Gemfibrozil has been used in the dog (200 mg/day) and cat (10 mg/kg q12h). Reported adverse effects include abdominal pain, vomiting, diarrhea, and abnormal liver function tests. The statins (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin) are hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors and therefore primarily suppress cholesterol metabolism. As a consequence of lower intracellular cholesterol concentrations, the hepatic LDL receptor is upregulated, thereby increasing the removal and clearance of LDL (VLDL remnant particles) from the circulation. In addition,

<sup>\*</sup>Information obtained from manufacturers' published information. Foods with less than 20% fat calories are listed.

the statins decrease hepatic production of VLDL. In humans the statins can lower triglyceride concentrations by 10% to 15%. Adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity.

Hypercholesterolemia is most likely associated with the presence of an underlying disease and generally resolves with control of the altered metabolic state. Unlike the situation with humans, hypercholesterolemia rarely poses a health risk to the dog or cat. Specific therapy is indicated only for those animals with a prolonged marked increase in the serum cholesterol concentration (i.e., more than 800 mg/dl) that may be associated with the development of atherosclerosis. Nutritional therapy with a lower-fat diet is the initial treatment of choice for severe hypercholesterolemia. The addition of soluble fiber to the diet may also help to reduce plasma cholesterol concentrations by as much as 10%. Soluble fiber interferes with the enteric reabsorption of bile acids. Consequently, the liver uses cholesterol to increase the synthesis of bile acids.

Pharmacologic agents that can be considered for the management of severe hypercholesterolemia include bile acid sequestrates, HMG-CoA reductase inhibitors, and probucol. Bile acid sequestrates are ion exchange resins that interrupt the enterohepatic circulation of bile acids. Decreased reabsorption of bile acids stimulates the liver to synthesize bile acids, utilizing intrahepatic cholesterol. Depletion of intrahepatic cholesterol stores stimulates the hepatic LDL receptor to increase the removal of LDL and HDL particles from the circulation. Cholestyramine (1 to 2 g, administered orally q12h) is effective for lowering cholesterol concentrations; however, its use has been associated with constipation, it interferes with the absorption of several oral medications, and it may increase hepatic VLDL synthesis, resulting in an increase in plasma triglyceride concentrations. It may also increase the dietary requirement for sulfur amino acids because they serve as precursors for taurine synthesis in the dog, which conjugates bile acids exclusively with taurine. In cats the requirement for dietary taurine may be similarly increased. HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis. The HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, and atorvastatin) are the most potent cholesterol-lowering agents and in humans may reduce cholesterol concentrations by 20% to 40%. Lovastatin (10 to 20 mg, administered orally q24h) may be tried in dogs with persistent, severe idiopathic hypercholesterolemia that does not respond to diet alone. Potential adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity. Lovastatin should not be administered to dogs with hepatic disease. Probucol is a cholesterollowering agent whose mechanism of action is not completely clear. Probucol is not widely recommended for the management of hypercholesterolemia because its effect on lowering cholesterol concentrations is variable and it has been associated with the development of arrhythmias.

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# CHAPTER Electrolyte Imbalances

#### CHAPTER OUTLINE

HYPERNATREMIA
HYPONATREMIA
HYPERKALEMIA
HYPOKALEMIA
HYPERCALCEMIA
HYPOCALCEMIA
HYPERPHOSPHATEMIA
HYPOPHOSPHATEMIA
HYPOMAGNESEMIA
HYPERMAGNESEMIA

#### **HYPERNATREMIA**

#### **Etiology**

Hypernatremia exists if the serum sodium concentration exceeds 160 mEq/L, although reference ranges may vary between laboratories. It most commonly develops after water loss exceeds sodium loss (Box 55-1). The water loss may be pure (i.e., not accompanied by a loss of electrolytes, such as that which occurs with diabetes insipidus), or it may be hypotonic (i.e., loss of both water and sodium but with the water loss predominating, such as that which occurs with gastrointestinal fluid loss and renal failure). Insufficient water intake or an abnormal thirst mechanism are usually facets of an excessive water loss. Rarely, hypernatremia may occur in animals with hypodipsia caused by neurologic disease, an abnormal thirst mechanism, or defective osmoregulation of vasopressin release.

Less commonly, hypernatremia develops after sodium retention, such as that which occurs with iatrogenic sodium overload or primary hyperaldosteronism. Primary hyperaldosteronism is caused by an aldosterone-secreting adrenal tumor or idiopathic bilateral adrenal hyperplasia but is rare in dogs and cats. Increased serum aldosterone concentrations cause variable hypernatremia, hypokalemia, and systemic hypertension.

#### **Clinical Features**

Clinical signs of hypernatremia originate in the central nervous system (CNS) and include lethargy, weakness, muscle fasciculations, disorientation, behavioral changes, ataxia, seizures, stupor, and coma. Clinical signs typically become apparent when the plasma osmolality exceeds 350 mOsm/kg (serum sodium concentration of greater than 170 mEq/L). Clinical signs are caused by neuronal dehydration. Hypernatremia and hyperosmolality cause fluid to shift from the intracellular to the extracellular space. As the brain shrinks, meningeal vessels are damaged and torn, causing hemorrhage, hematoma, venous thrombosis, infarction of cerebral vessels, and ischemia. This gradient flow of water from the intracellular to the extracellular compartment often maintains adequate skin turgor and gives a false impression of hydration, even though the animal has experienced a detrimental loss of fluid.

The severity of clinical signs is related to the absolute increase in serum sodium concentration and especially the rapidity of onset of hypernatremia and hyperosmolality. Clinical signs usually do not develop until the serum sodium concentration approaches 170 mEq/L. If hypernatremia is rapid in onset, clinical signs may develop at a lower sodium concentration, and vice versa. With a gradual increase in the serum sodium concentration, the cells in the CNS can produce osmotically active solutes (idiogenic osmoles) intracellularly to reestablish osmotic equilibration between the extracellular and intracellular compartments, thereby minimizing cell shrinkage.

#### Diagnosis

Measurement of the serum sodium concentration identifies hypernatremia. After it has been identified, the underlying cause should be sought. Careful evaluation of the history, physical examination findings, and results of routine clinical pathologic tests (i.e., complete blood count [CBC], serum biochemistry panel, urinalysis) usually yields clues to the cause. Evaluation of the urine specific gravity is especially helpful. Hypernatremia and hyperosmolality stimulate the release of vasopressin, resulting in hypersthenuria. A urine



#### Causes of Hypernatremia in Dogs and Cats

#### **Caused by Pure Water Loss**

Central diabetes insipidus\*
Nephrogenic diabetes insipidus\*
Hypodipsia-adipsia
Neurologic disease

Abnormal thirst mechanism

Defective osmoregulation of vasopressin release

Inadequate access to water

High environmental temperature (heat stroke) Fever

#### **Hypotonic Fluid Loss**

Gastrointestinal fluid loss\*

Vomiting

Diarrhea

Chronic renal failure\*

Polyuric acute renal failure\*

Osmotic diuresis

Diabetes mellitus

Mannitol infusion

Divretic administration

Postobstructive diuresis

Cutaneous burns

Third-space loss

**Pancreatitis** 

**Peritonitis** 

#### **Excess Sodium Retention**

Primary hyperaldosteronism latrogenic

Salt poisoning

Hypertonic saline infusion

Sodium bicarbonate therapy

Parenteral nutrition\*

Modified from DiBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid*, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders/Elsevier. specific gravity of less than 1.008 in a dog or cat with hypernatremia is consistent with central or nephrogenic diabetes insipidus. A urine specific gravity of more than 1.030 in a dog and 1.035 in a cat implies a normal vasopressin–renal tubular axis and indicates the existence of sodium retention, primary hypodipsia-adipsia, or gastrointestinal or insensible water loss. A urine specific gravity of between 1.008 and 1.030 (dog) or of 1.035 (cat) indicates the presence of partial vasopressin deficiency or an impaired renal tubular response to vasopressin, most likely secondary to a primary renal disorder.

#### **Treatment**

The goal in treating hypernatremia is to restore the extracellular fluid (ECF) volume to normal and correct water deficits at a fluid rate that avoids significant complications and to identify and correct the underlying cause of the hypernatremia. The initial priority is to restore ECF volume to normal. In animals with modest volume contraction (e.g., tachycardia, dry mucous membranes, slow skin turgor), fluid deficits should be corrected with 0.45% saline supplemented with an appropriate amount of potassium (Table 55-1). With severe dehydration 0.9% saline solution, plasma, or whole blood should be used to expand vascular volume. In deficit replacement rapid administration of fluids is contraindicated unless there are signs of significant hypovolemia. Any fluid should be administered in a volume only large enough to correct hypovolemia. Worsening neurologic status or sudden onset of seizures during fluid therapy is generally indicative of cerebral edema and the need for hypertonic saline solution or mannitol therapy. Once ECF deficits have been replaced, the serum sodium (Na) concentration should be reevaluated and water deficits corrected if hypernatremia persists. An approximation of the water deficit in liters may be calculated using the following formula:

#### $0.3 \times \text{body weight (kg)} \times [(\text{measured Na}^+ - 140)/140]$

Because the brain adjusts to hypertonicity by increasing the intracellular solute content via the accumulation of "idiogenic osmoles," the rapid repletion of body water with ECF dilution causes translocation of water into cells and may



TABLE 55-1

Guidelines for Potassium Supplementation in IV Fluids

SERUM K* (mEq/L)	TOTAL mEq OF K+ /LITER OF FLUIDS	MAXIMUM FLUID INFUSION RATE (ml/kg/h)*
>3.5	20 mEq	25
3.0-3.5	30 mEq	16
2.5-3.0	40 mEq	12
2.0-2.5	60 mEq	8
<2.0	80 mEq	6

<sup>\*</sup> Total hourly potassium administration should not exceed 0.5 mEq/kg body weight.

<sup>\*</sup> Common causes.

cause cerebral edema. If slower water repletion is undertaken, brain cells lose the accumulated intracellular solutes and osmotic equilibration can occur without cell swelling.

Maintenance crystalloid solutions (e.g., half-strength [0.45%] saline solution with 2.5% dextrose or half-strength lactated Ringer's solution with 2.5% dextrose) should be used to correct the water deficit in hypernatremic animals with normal perfusion and hydration and should also be used in dehydrated animals with persistent hypernatremia after the correction of fluid deficits. D₅W solution can be substituted for maintenance crystalloid solutions if the hypernatremia does not abate after 12 to 24 hours of fluid therapy.

Oral fluid administration is preferable for correcting water deficits, with fluid administered through an intravenous (IV) route if oral administration is not possible. The water deficit should be replaced slowly. Approximately 50% of the water deficit should be corrected in the first 24 hours, with the remainder corrected over the ensuing 24 to 48 hours. The serum sodium concentration should decline slowly, preferably at a rate of less than 1 mEq/L/hour. A gradual reduction in the serum sodium concentration minimizes the fluid shift from the extracellular to the intracellular compartment, thereby minimizing neuronal cell swelling and cerebral edema and increasing intracranial pressure. A deterioration in CNS status after the start of fluid therapy indicates the presence of cerebral edema and the immediate need to reduce the rate of fluid administration. Frequent monitoring of serum electrolyte concentrations, with appropriate adjustments in the type of fluid administered and rate of fluid administration, is important in the successful management of hypernatremia.

On rare occasions a hypernatremic animal presents with an increase in the ECF volume. Such animals are difficult to treat. The goal is to lower the serum sodium concentration without exacerbating an increase in the ECF volume and causing pulmonary congestion and edema. To slowly correct hypernatremia in these animals, the clinician should administer loop diuretics (e.g., furosemide, 1 to 2 mg/kg orally or intravenously q8-12h) to promote sodium loss in the urine, and this is done in conjunction with the judicious administration of  $D_{\bar{5}}W$ .

#### HYPONATREMIA

#### Etiology

Hyponatremia is present if the serum sodium concentration is less than 140 mEq/L, although reference ranges may vary between laboratories. It can result from excessive sodium loss, primarily through the kidney, or from increased water conservation, or both. The latter condition may be an appropriate response to a reduction in the ECF volume or may be inappropriate (e.g., syndrome of inappropriate antidiuretic hormone secretion). In most cases hyponatremia results from abnormalities in water balance (principally a defect in renal water excretion) rather than from abnormalities in



Causes of Hyponatremia in Dogs and Cats

#### With Normal Plasma Osmolality

Hyperlipidemia

Hyperproteinemia

#### With High Plasma Osmolality

Hyperglycemia\* Mannitol infusion

#### With Low Plasma Osmolality

And hypervolemia

Advanced liver failure\*

Advanced renal failure\*

Nephrotic syndrome\*

Congestive heart failure

And normovolemia

Primary polydipsia

Inappropriate antidiuretic hormone (ADH) secretion

(SIADH)

Myxedema coma of hypothyroidism

latrogenic

Hypotonic fluid administration

Antidiuretic drugs (e.g., barbiturates, β-adrenergics)

And hypovolemia

Hypoadrenocorticism\*

Gastrointestinal fluid loss\*

Third-space loss

Pleural effusions (e.g., chylothorax)

Peritoneal effusions

**Pancreatitis** 

Cutaneous burns

Diuretic administration

Modified from DiBartola SP: Disorders of sodium and water: hypernatremia and hyponatremia. In DiBartola SP, editor: *Fluid, electrolyte and acid-base disorders in small animal practice,* ed 3, St Louis, 2006, Saunders/Elsevier.

sodium balance. Causes of hyponatremia in dogs and cats are listed in Box 55-2.

Hyponatremia must be differentiated from pseudohyponatremia, which is a decrease in the serum sodium concentration as a result of laboratory methodology in the presence of normal plasma osmolality. Pseudohyponatremia occurs in the presence of hyperlipidemia or severe hyperproteinemia. An increase in the concentration of triglycerides or proteins in plasma reduces the sodium concentration in the total plasma volume, but the sodium concentration in plasma water remains the same. Methods that measure the amount of sodium in a specific volume of plasma (e.g., flame photometry) result in falsely low sodium values, whereas methodologies that determine the sodium concentration in the aqueous phase of plasma (e.g., direct potentiometry using ion-selective electrodes) yield an accurate sodium value. Pseudohyponatremia can usually be identified if the method used to measure the sodium concentration is known, a blood

sample is examined for the presence of gross lipemia, and a CBC and serum biochemistry panel are performed.

Hyponatremia may also occur after there is an increase in the concentration of osmotically active solutes (e.g., glucose, mannitol) in the ECF. An increase in the concentration of osmotically active solutes in the ECF causes a fluid shift from the intracellular to the extracellular compartment and a corresponding decrease in the serum sodium concentration. For example, the serum sodium concentration decreases approximately 1.6 mEq/L for every 100 mg/dl increase in the serum glucose concentration, and this decrease may become more severe when the blood glucose concentration exceeds 500 mg/ dl. Estimation of the plasma osmolality is helpful in differentiating the cause of hyponatremia. Hyponatremia is usually associated with hyposmolality (less than 290 mOsm/kg), whereas pseudohyponatremia is associated with normal plasma osmolality, and hyponatremia caused by an increase in osmotically active solutes in the ECF is associated with hyperosmolality. Plasma osmolality can be estimated using the following formula:

Plasma osmolality (mOsm/kg) =  $(2 \times Na [mEq/L]) +$ 

$$\frac{Glucose~(mg/dl)}{18} + \frac{Urea~nitrogen~(mg/dl)}{2.8}$$

Normal plasma osmolality in dogs and cats is approximately 280 to 310 mOsm/kg.

#### **Clinical Features**

Clinical signs of hyponatremia include lethargy, anorexia, vomiting, weakness, muscle fasciculations, disorientation, seizures, and coma. CNS signs are the most worrisome and develop as changes in plasma osmolality cause fluid to shift from the extracellular to the intracellular space, resulting in neuronal swelling and lysis. The onset and severity of clinical signs depend on the rapidity with which the hyponatremia develops as well as on the degree of hyponatremia. The more chronic the hyponatremia and the more slowly it develops, the more capable the brain is of compensating for changes in osmolality through the loss of potassium and organic osmolytes from cells. Clinical signs develop when the decrease in plasma osmolality occurs faster than the brain's defense mechanisms can counter the influx of water into the neurons.

#### Diagnosis

Hyponatremia is readily evident from measurement of serum electrolyte concentrations. However, hyponatremia must be differentiated from pseudohyponatremia (discussed in a previous section). Hyponatremia is not a diagnosis per se but rather a manifestation of an underlying disorder. As such, a diagnostic evaluation to identify the cause, as well as appropriate therapy to correct the hyponatremia, should be initiated. In most dogs and cats the cause of hyponatremia is readily apparent after evaluation of the history, physical examination findings, CBC, serum biochemistry panel, and urinalysis findings, but further diagnostic tests may be neces-

sary. Careful assessment of the urine specific gravity; the hydration status of the animal; and, if necessary, the fractional excretion of sodium (FE<sub>Na</sub>) help localize the problem (Fig. 55-1). The FE<sub>Na</sub> can be determined by first measuring the urine ( $U_{Na}$ ) and plasma ( $P_{Na}$ ) sodium and urine ( $U_{Cr}$ ) and plasma ( $P_{Cr}$ ) creatinine concentrations and then applying the following formula:

$$FE_{Na} = (U_{Na}/P_{Na}) \times (P_{Cr}/U_{Cr}) \times 100$$

#### **Treatment**

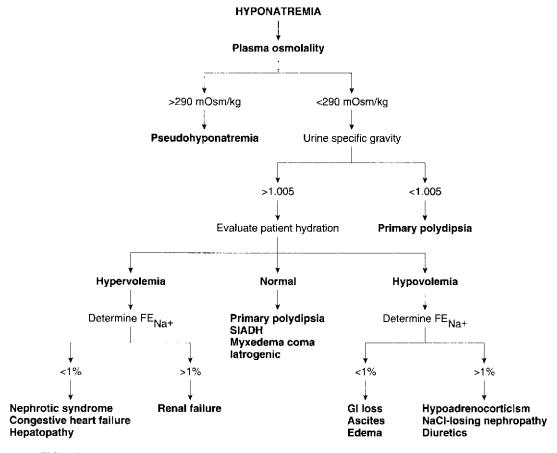
The goals of therapy are to treat the underlying disease and, if necessary, to increase the serum sodium concentration and plasma osmolality. The goal of treatment directed at the hyponatremia is to correct body water osmolality and restore cell volume to normal by raising the ratio of sodium to water in ECF using IV fluid therapy, water restriction, or both. The increase in ECF osmolality draws water from cells and therefore reduces their volume. The approach to treatment and the type of fluid used depend on the underlying etiology, the severity of the hyponatremia, and the presence or absence of clinical signs (Table 55-2). Chronic hyponatremia in an asymptomatic animal is best treated conservatively. Lactated Ringer's or Ringer's solution can be used for mild hyponatremia (serum sodium concentration of more than 135 mEq/ L) and physiologic saline solution for more severe hyponatremia (serum sodium concentration of less than 135 mEq/ L). Physiologic saline solution is typically used in symptomatic animals with severe hyponatremia.

Fluid and electrolyte balance should gradually be restored over 24 to 48 hours, with periodic assessment of serum electrolyte concentrations. The more acute and severe the hyponatremia, the more slowly the serum sodium concentration should be corrected. A rapid increase in the serum sodium concentration to levels greater than 125 mEq/L is potentially dangerous and should be avoided in animals with acute, severe hyponatremia (serum sodium concentration of less than 120 mEq/L) and neurologic signs. For these animals the serum sodium concentration should be gradually increased to 125 mEq/L or higher over 6 to 8 hours. Because loss of brain solute represents one of the compensatory mechanisms for preserving brain cell volume during dilutional states, an increase in serum sodium concentration toward normal is relatively hypertonic to brain cells that are partially depleted of solute as a result of hyponatremia. Consequently, raising the serum sodium concentration rapidly to greater than 125 mEq/L can cause CNS damage. Dietary sodium restriction (e.g., Prescription Diet h/d, Hill's Pet Products) and diuretic therapy should be considered in edematous animals.

#### HYPERKALEMIA

#### Etiology

Hyperkalemia is present if the serum potassium concentration exceeds 5.5 mEq/L, although reference ranges may vary



**FIG 55-1**Diagnostic approach to hyponatremia. *FE*<sub>No</sub>, Fractional excretion of sodium. (Adapted from DiBartola SP: Hyponatremia, *Vet Clin North Am* 19:215, 1989.)

between laboratories. Hyperkalemia can develop after an increased potassium intake (uncommon), after a compartmental shift in potassium from the intracellular to extracellular space (uncommon), or as a result of impaired potassium excretion in the urine (common; Box 55-3). Impaired urinary excretion of potassium is usually caused by renal dysfunction or hypoadrenocorticism. Iatrogenic-induced hyperkalemia is also common in dogs and cats. Pseudohyperkalemia refers to an increase in potassium in vitro and can occur in the setting of severe hypernatremia (if dry reagent methodologies are used), leukocytosis (white blood cell count of more than 100,000/ $\mu$ l), and thrombocytosis (more than 1 × 10<sup>6</sup>/ μl); if the blood specimen has been obtained from fluid lines or catheters contaminated with potassium-containing fluids; and in the setting of hemolysis in Akitas (and possibly Shiba Inus and Kindos) and in English Springer Spaniels with phosphofructokinase deficiency.

#### **Clinical Features**

The clinical manifestations of hyperkalemia reflect changes in cell membrane excitability and the magnitude and rapidity of onset of hyperkalemia. Mild-to-moderate hyperkalemia (serum potassium concentration of less than 6.5 mEq/L) is typically asymptomatic. Generalized skeletal muscle weak-

ness develops as the hyperkalemia worsens. Weakness occurs after a hyperkalemia-induced decrease in the resting cell membrane potential to the level of the threshold potential, thereby impairing repolarization and subsequent cell excitation. The most prominent manifestations of hyperkalemia are cardiac in nature. Hyperkalemia causes decreased myocardial excitability, an increased myocardial refractory period, and slowed conduction, effects that may cause potentially life-threatening cardiac rhythm disturbances (Box 55-4).

#### Diagnosis

Measurement of the serum potassium concentration or electrocardiography can identify hyperkalemia. Once it has been identified, a careful review of the history, physical findings, CBC, serum biochemistry panel, and urinalysis usually yields clues to the cause. The most common causes for hyperkalemia in the dog and cat are iatrogenic, most notably excessive potassium administration in IV fluids; renal dysfunction, especially acute oliguric-anuric renal failure, urethral obstruction (tomcats), and rupture within the urinary system leading to uroabdomen; and hypoadrenocorticism. It can be a diagnostic challenge to differentiate renal dysfunction from hypoadrenocorticism because both disorders can result in a similar clinical picture. An adrenocorticotropic



	ELECTROLYTE CONCENTRATION (mEq/L)					
SOLUTION	Na	K	CI	BUFFER (mEq/L)	OSMOLALITY (mOsm/L)	CALORIES (kcal/L)
Electrolyte Replacement Solutions						
Lactated Ringer's	130	4	109	Lactate 28	272	9
Ringer's	1 <i>47</i>	4	156		310	_
Normal saline	154	_	154	_	308	_
Normosol R	140	5	98	Acetate 27	296	18
Maintenance Solutions						
21/2% Dextrose/0.45% saline	77	_	77	_	280	85
2 <sup>1</sup> / <sub>2</sub> % Dextrose/ <sup>1</sup> / <sub>2</sub> strength LRS	65	2	55	Lactate 14	263	89
Normosol M	40	13	40	Acetate 16	112	_
Normosol M in 5% dextrose	40	13	40	Acetate 16	364	1 <i>75</i>
Colloidal Solutions						
Dextran 70 (6% w/v in 0.9% saline)	154		154	<del></del>	310	
Hetastarch 450/0.7	154	_	154	_	310	_
Plasma (average values, dog)	145	4	105	24	300	
Other						
5% Dextrose in water	_	_	_	_	252	170

Modified from DiBartola SP, Bateman S: Introduction to fluid therapy. In DiBartola SP, editor: Fluid, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders Elsevier, p. 333.

Na, Sodium; K, potassium; Cl, chloride; LRS, lactated Ringer's solution.



BOX 55-3

Causes of Hyperkalemia in Dogs and Cats

#### Transcellular Shifts (ICF to ECF)

Metabolic and respiratory acidosis Insulin deficiency—DKA Acute tumor lysis syndrome Reperfusion post thrombus dissolution

#### **Decreased Urinary Excretion**

Hypoadrenocorticism\*

Acute oliguric-anuric renal failure\*
End-stage chronic renal failure
Urethral obstruction\*
Ruptured bladder—uroabdomen\*
Selected gastroenteritis (e.g., trichuriasis, salmonellosis)
Chylothorax with repeated pleural fluid drainage
Hyporeninemic hypoaldosteronism

#### latrogenic†

Potassium-sparing diuretics (e.g., spironolactone)
Angiotensin-converting enzyme inhibitors (e.g., enalapril)
Angiotensin-receptor blockers (e.g., losartin)
β-blockers (e.g., propranolol)
Cardiac glycosides (e.g., digitalis)
Prostaglandin inhibitors (e.g., indomethacin)
α-Adrenergic agonists (e.g., phenylpropanolamine)
Cyclosporine
Nonsteroidal antiinflammatory drugs

Excessive administration of potassium-containing fluids\*

#### **Pseudohyperkalemia**

Hemolysis (Akita) Thrombocytosis (>10°/µl) Leukocytosis (>10°/µl) Hypernatremia (dry reagent methods)

Modified from DiBartola SP, Autran de Morais H: Disorders of potassium: hypokalemia and hyperkalemia. In DiBartola SP, editor: Fluid, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders Elsevier. ICF, Intracellular fluid; ECF, extracellular fluid; DKA, diabetic ketoacidosis.

<sup>\*</sup> Common causes.

<sup>†</sup>Requires contributing factors to cause hyperkalemia.

hormone (ACTH) stimulation test is needed to confirm hypoadrenocorticism. Small rents in the urinary bladder can be difficult to identify, and contrast-enhanced radiographic studies or surgical exploration is frequently necessary to confirm their presence.

#### **Treatment**

For most animals therapy for hyperkalemia is directed at treating the underlying cause. Symptomatic therapy for



BOX 55-4

Electrocardiographic Alterations Associated with Hyperkalemia and Hypokalemia in Dogs and Cats

#### Hyperkalemia

Serum potassium: 5.6-6.5 mEq/L

Bradycardia Tall, narrow T waves

Serum potassium: 6.6-7.5 mEq/L Decreased R-wave amplitude

Prolonged QRS interval
Serum potassium: 7.0-8.5 mEa/L

Decreased P-wave amplitude
Prolonged P-R interval

Serum potassium: >8.5 mEq/L

Invisible P wave

Deviation of ST segment Complete heart block Ventricular arrhythmias

Cardiac arrest

#### Hypokalemia

Ventricular

Depressed T-wave amplitude
Depressed ST segment
Prolonged QT interval
Prominent U wave
Arrhythmias
Supraventricular

hyperkalemia should be initiated if the serum potassium concentration is greater than 7 mEq/L or if pronounced cardiac toxicity (i.e., complete heart block, premature ventricular contractions, arrhythmias) is identified on an electrocardiogram (ECG; Table 55-3). The rapid institution of therapy in animals with marked hyperkalemia could mean the difference between life and death. The goal of symptomatic therapy is to reverse the cardiotoxic effects of hyperkalemia and, if possible, reestablish normokalemia. Asymptomatic animals with normal urine output and chronic hyperkalemia of less than 7 mEq/L may not require immediate treatment, but a search for the underlying cause should be initiated.

IV fluid administration in amounts designed to correct fluid deficits and cause volume expansion rehydrates the animal, improves renal perfusion and potassium excretion, and dilutes the blood potassium concentration. Physiologic saline solution is the fluid of choice for this purpose. Potassium-containing fluids (e.g., lactated Ringer's solution) can be used if physiologic saline solution is not available because the low potassium concentration in these fluids (see Table 55-2) in relation to that in blood will still have a dilutional effect on the blood potassium concentration. Dextrose can be added to the fluids to make a 5% to 10% dextrosecontaining solution, or 1 to 2 ml/kg of 50% dextrose can be administered by slow IV bolus. Dextrose stimulates insulin secretion, which in turn promotes the movement of glucose and potassium from the extracellular to the intracellular space. Fluids containing more than 5% dextrose should be given into a central vein to minimize the risk of phlebitis.

Rarely, additional therapy may be required to block the cardiotoxic effects of hyperkalemia (see Table 55-3). Sodium bicarbonate and regular insulin given with dextrose act to shift potassium from the extracellular to the intracellular space. IV calcium infusions block the effects of hyperkalemia on cell membranes but do not lower the blood potassium concentration. These therapies constitute aggressive, short-term, life-saving measures that can reestablish normal cardiac conduction until more conventional therapy (i.e., IV fluids) has the time to become effective.



**TABLE 55-3** 

Treatment Options for Hyperkalemia in the Dog and Cat

TREATMENT	DOSAGE	ROUTE OF ADMINISTRATION	DURATION OF EFFECT
Physiologic saline	≥60-100 ml/kg/day	IV	Hours
Dextrose	5%-10% in IV fluids or	IV, continuous	Hours
	1-2 ml of 50% dextrose/kg	IV, slow bolus	Hours
Regular insulin and dextrose	0.5-1.0 U/kg in parenteral fluids plus	IV	Hours
	2 g dextrose/U insulin administered	IV	Monitor blood glucose
Sodium bicarbonate	1-2 mEq/kg	IV, slow bolus	Hours
10% Calcium gluconate	2-10 ml	IV, slow bolus	30-60 min. Monitor heart

#### HYPOKALEMIA

#### Etiology

Hypokalemia is present when the serum potassium concentration is less than 4.0 mEq/L, although reference ranges may vary between laboratories. Hypokalemia can develop after decreased dietary potassium intake (uncommon), translocation of potassium from the ECF to the intracellular fluid (common), or increased potassium loss in urine or gastrointestinal secretions (common; Box 55-5). Iatrogenic hypokalemia is also common in dogs and cats. Pseudohypokalemia is uncommon and depends on the method used to measure the serum potassium concentration. Hyperlipidemia, hyperproteinemia (more than 10 g/dl), hyperglycemia (more than 750 mg/dl), and azotemia (urea nitrogen concentration of more than 115 mg/dl) can potentially cause pseudohypokalemia.



BOX 55-5

Causes of Hypokalemia in Dogs and Cats

#### Transcellular Shifts (ECF to ICF)

Metabolic alkalosis Hypokalemic periodic paralysis (Burmese cats)

#### **Increased Loss**

Gastrointestinal fluid loss\*
Chronic renal failure, especially in cats\*
Diabetic ketoacidosis\*
Diet-induced hypokalemic nephropathy in cats
Distal (type I) renal tubular acidosis
Proximal (type II) renal tubular acidosis after sodium bicarbonate treatment
Postobstructive diuresis
Primary hyperaldosteronism
Hyperthyroidism
Hypomagnesemia

#### latrogenic\*

Postassium-free fluid administration (e.g., 0.9% saline) Parenteral nutritional solutions Insulin and glucose-containing fluid administration Sodium bicarbonate therapy Loop (e.g., furosemide) and thiazide diuretics Low dietary intake

#### **Pseudohypokalemia**

Hyperlipidemia (dry reagent methods; flame photometry) Hyperproteinemia (dry reagent methods; flame photometry) Hyperglycemia (dry reagent methods) Azotemia (dry reagent methods)

Modified from DiBartola SP, Autran de Morais H: Disorders of potassium: hypokalemia and hyperkalemia. In DiBartola SP, editor: Fluid, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders/Elsevier.

ECF, Extracellular fluid; ICF, intracellular fluid. \*Common causes.

#### **Clinical Features**

Most dogs and cats with mild to moderate hypokalemia (i.e., 3.0 to 4.0 mEq/L) are asymptomatic. Clinically severe hypokalemia primarily affects the neuromuscular and cardiovascular systems, owing to the hypokalemia-induced initial hyperpolarization followed by hypopolarization of cell membranes. The most common clinical sign of hypokalemia is generalized skeletal muscle weakness. In cats ventroflexion of the neck (see Chapter 72), forelimb hypermetria, and a broad-based hindlimb stance may be observed. The timing of the onset of hypokalemia-induced weakness is extremely variable among animals. Cats seem more susceptible than dogs to the deleterious effects of hypokalemia. In dogs signs may not be evident until the serum potassium concentration is less than 2.5 mEq/L, whereas in cats signs can be seen when the serum potassium concentration is between 3 and 3.5 mEa/L.

Cardiac consequences of hypokalemia include decreased myocardial contractility, decreased cardiac output, and disturbances in cardiac rhythm. Cardiac disturbances assume a variable clinical expression, often evidenced only by electrocardigraphy (see Box 55-4). Other metabolic effects of hypokalemia include hypokalemic nephropathy, which is characterized by chronic tubulointerstitial nephritis, impaired renal function, and azotemia and manifested clinically as polyuria, polydipsia, and impaired urine concentrating capability; hypokalemic polymyopathy, which is characterized by increased serum creatine kinase activity and electromyographic abnormalities; and paralytic ileus, manifested clinically as abdominal distention, anorexia, vomiting, and constipation. Hypokalemic nephropathy and polymyopathy are most notable in cats.

#### **Diagnosis**

Measurement of the serum potassium concentration identifies hypokalemia. Once it has been identified, a careful review of the history, physical findings, CBC, serum biochemistry panel, and urinalysis findings usually provides clues to the cause (see Box 55-5). If the cause is not readily apparent after review of this information, other, less likely causes for hypokalemia should be considered, such as renal tubular acidosis or another renal potassium-wasting disorder, primary hyperaldosteronism, and hypomagnesemia. To help differentiate renal and nonrenal sources of potassium loss, the clinician may need to determine the fractional excretion of potassium determined on the basis of a single urine and serum potassium and creatinine concentration or determine 24-hour urine potassium excretion (see Chapter 42).

#### **Treatment**

Therapy is indicated if the serum potassium concentration is less than 3 mEq/L, if clinical signs related to hypokalemia are present, or if a serum potassium loss is anticipated (e.g., insulin therapy in diabetic ketoacidosis [DKA]) and the animal's ability to compensate for the loss is impaired. The goal of therapy is to reestablish and maintain normokalemia without inducing hyperkalemia.

Potassium supplements should be given orally whenever possible. Oral potassium supplements come in the form of elixirs, wax-matrix tablets, and microencapsulated slowrelease formulations. Problems with oral preparations include poor palatability, which can be minimized by mixing them with food, and gastrointestinal tract irritation, which may cause vomiting, diarrhea, and melena. Two products that are well accepted by most dogs and cats and that have minimal gastrointestinal tract side effects are potassium gluconate elixir (Kaon Elixir, Adria Laboratories) and potassium gluconate prepared in a palatable protein base (Tumil-K, Virbac). The recommended dose for these products is 2.2 mEq of potassium per 100 calories of required energy intake per day or 2 mEq of potassium per 4.5 kg of body weight twice a day. Subsequent adjustments in dosage are made on the basis of clinical response and serum potassium concentrations. Bananas are also a good source of potassium. Ten inches (25 cm) of banana contains approximately 10 mEq of potassium.

Parenteral potassium supplementation is indicated if oral administration is not possible (e.g., vomiting, anorexia). Potassium chloride is the compound most commonly used, in part to help promote chloride as well as potassium repletion. IV administration is preferred, although potassium chloride can be given subcutaneously as long as the concentration of potassium does not exceed 30 mEq/L. In dogs and cats with normal renal function, the maintenance amount of potassium supplementation is approximately 20 mEq/L of fluids. The initial amount of potassium added to fluids depends on the animal's serum potassium concentration (see Table 55-1) and the amount of potassium already present in the fluids (see Table 55-2). The rate of IV potassium administration should not exceed 0.5 mEq/kg/hour.

It is difficult to estimate the amount of potassium required to reestablish normal potassium balance on the basis of the serum potassium concentration because potassium is primarily an intracellular cation. As such, serial measurement of the serum potassium concentration is important during treatment and should initially be done every 6 to 12 hours depending on the severity of the hypokalemia and the rate of potassium administration. Adjustments in potassium therapy should be made accordingly, with the goal of establishing a normal serum potassium concentration and then maintaining the serum potassium concentration in the normal range as treatment is withdrawn. Clinical signs of hypokalemia usually resolve within 1 to 5 days after correction of hypokalemia. Depending on the underlying cause, long-term oral potassium supplementation may be required to prevent recurrence of hypokalemia.

#### HYPERCALCEMIA

#### **Identification**

Hypercalcemia is present if the serum calcium concentration is greater than 12 mg/dl or the serum ionized calcium concentration is greater than 1.45 mmol/L, although reference

ranges may vary between laboratories. The serum total and ionized calcium concentration is higher in puppies than in adult dogs. A mild increase in the serum total calcium (i.e., less than 13 mg/dl), ionized calcium (i.e., less than 1.55 mmol/L), and phosphorus (i.e., less than 10 mg/dl) concentrations in a clinically healthy puppy, together with an increase in the serum alkaline phosphatase activity and normal urea nitrogen and creatinine concentrations, should be considered normal. The serum total calcium concentration does not fluctuate with age in cats, but the serum ionized calcium concentration may be higher (less than 0.1 mmol/L) in cats younger than 2 years of age compared with results in older cats.

Most automated and in-house serum chemistry analyzers measure the total serum calcium concentration, which consists of biologically active, ionized calcium (55%); proteinbound calcium (35%); and calcium complexes (10%). A drawback to this is that alterations in the plasma protein concentration may alter the total serum calcium concentration, yet the ionized calcium concentration remains normal. For this reason the serum albumin and total protein concentrations should be measured when determining the total serum calcium concentration in the dog. Simple quantitative changes in the albumin and total plasma proteins do not cause hypocalcemia or hypercalcemia in dogs, even though the total serum calcium levels may appear to be low or high on the biochemistry panel. The following formulas have been used to estimate the total serum calcium concentration in dogs with hypoalbuminemia or hypoproteinemia:

Adjusted calcium (mg/dl) = Serum calcium (mg/dl) - Serum albumin (g/dl) + 3.5

or

Adjusted calcium (mg/dl) = Serum calcium (mg/dl) –  $(0.4 \times \text{Serum total protein } [g/dl]) + 3.3$ 

The formulas are not used in dogs younger than 24 weeks of age, because high values may be obtained, nor are they used in cats, because there is no linear relationship between serum total calcium and serum albumin and total protein concentration in cats. These formulas yield a rough estimate of the total serum calcium concentration and were developed without verification by serum ionized calcium measurements. Subsequent studies identified a poor correlation between the adjusted total calcium results and the corresponding serum ionized calcium concentration, suggesting that adjusted total serum calcium concentrations are not reliable indicators of calcium homeostasis.

The biologically active, ionized fraction of calcium can be determined directly, which bypasses the influence of plasma proteins on the total serum calcium concentration. Ionized calcium measurements are generally superior to serum total calcium measurements for assessing calcium in dogs and cats. Automated equipment that uses a calcium ion-selective electrode allows accurate measurement of ionized calcium in blood, plasma, or serum. Ionized calcium results can be affected by many variables, including method of sample

collection (samples collected anaerobically provide more precise results); the amount and type of heparin, if used (may underestimate or overestimate ionized calcium results); and change in sample pH (ionized calcium increases as pH decreases). Protocols established by the clinical chemistry laboratory for submitting blood samples for ionized calcium determination should be followed to ensure accurate results.

#### **Etiology**

Hypercalcemia is uncommon in dogs and cats. Persistent hypercalcemia usually results from increased calcium resorption from bone or kidney or increased calcium absorption from the gastrointestinal tract. Humoral hypercalcemia of malignancy (HHM), the most common cause of hypercalcemia, occurs when the tumor produces substances that promote osteoclastic activity and renal calcium reabsorption. These substances include parathyroid hormone (PTH); parathyroid hormone-related peptide (PTHrP); 1,25dihydroxyvitamin D; cytokines, such as interleukin-1 and tumor necrosis factor; prostaglandins; and humoral factors that stimulate renal 1-α-hydroxylase. Tumors may also induce hypercalcemia by local osteolytic activity after they metastasize to bone. Less commonly, hypercalcemia develops from impaired loss of calcium from the serum (e.g., reduced glomerular filtration) or reduced plasma volume (e.g., dehydration).

The list of differential diagnoses for hypercalcemia is relatively short in dogs and cats (see Table 50-2). In the dog HHM (especially lymphoma), hypoadrenocorticism, chronic renal failure, hypervitaminosis D, and primary hyperparathyroidism are the most common diagnoses. In the cat idiopathic hypercalcemia, hypercalcemia of malignancy (especially lymphoma and squamous cell carcinoma), chronic renal failure, and primary hyperparathyroidism are the most common diagnoses. Calcium oxalate urolithiasis and consumption of acidifying diets are commonly identified in cats with hypercalcemia, but their role, if any, in causing the disorder is unknown.

Hypercalcemia can develop in dogs and cats with chronic and, less commonly, acute renal failure. The pathogenesis of hypercalcemia associated with renal failure is complicated. The development of autonomously functioning parathyroid glands or an alteration of the set point for PTH secretion after the prolonged stimulation of renal secondary hyperparathyroidism, decreased PTH degradation by renal tubular cells, increased PTH-mediated intestinal absorption of calcium, increased PTH-mediated bone resorption, decreased renal excretion of calcium, and increased protein-bound or complexed fractions of calcium are believed to contribute to the hypercalcemia of renal failure. Prolonged hypercalcemia, especially in conjunction with concurrent high-normal to increased serum phosphorus concentration, can also cause renal insufficiency and azotemia. Determining whether the renal failure is primary or secondary in a dog with hypercalcemia, hyperphosphatemia, and azotemia poses an interesting diagnostic challenge (see the diagnosis section).

#### **Clinical Features**

Although all tissues can be affected by hypercalcemia, the neuromuscular, gastrointestinal, renal, and cardiac systems are the most important clinically. Secondary nephrogenic diabetes insipidus, loss of the renal concentration gradient, and metastatic mineralization of the kidney cause polyuria and polydipsia. Decreased excitability of the central and peripheral nervous systems occurring in conjunction with decreased excitability of gastrointestinal smooth muscle causes lethargy, anorexia, vomiting, constipation, weakness, and (rarely) seizures. In rare instances cardiac arrhythmias may develop in animals with severe hypercalcemia (i.e., more than 18 mg/dl). Prolongation of the PR interval and shortening of the QT interval may be found on electrocardiographic readings recorded in animals with milder hypercalcemia.

Clinical signs are often absent with mild increases in the serum calcium concentration, and hypercalcemia is discovered only after a serum biochemistry panel is performed, often for unrelated reasons. When clinical signs do develop, they initially tend to be insidious in onset. The severity of clinical signs depends in part on the severity, rate of onset, and duration of the hypercalcemia. Clinical signs become more severe as the magnitude of the hypercalcemia increases, regardless of the rate of onset or duration. Clinical signs are usually mild with serum calcium concentrations less than 14 mg/dl, are readily apparent with concentrations greater than 14 mg/dl, and become potentially life-threatening (i.e., cardiac arrhythmias) when the serum calcium concentration exceeds 18 to 20 mg/dl. Clinical signs resulting from the development of calcium uroliths may also occur.

#### **Diagnosis**

Hypercalcemia should always be reconfirmed, preferably from a nonlipemic blood sample obtained from the dog or cat following a 12-hour fast, before embarking on an extensive diagnostic evaluation. Results of a CBC, serum biochemistry panel, and urinalysis, in conjunction with the history and physical examination findings, often provide clues to the diagnosis (see Table 50-2). Special attention should be paid to the serum electrolytes and renal parameters. Hypoadrenocorticism-induced hypercalcemia typically occurs in conjunction with mineralocorticoid deficiency; hyponatremia, hyperkalemia, and prerenal azotemia should be present. The serum phosphorus concentration is in the lower half of the normal range or low with HHM and primary hyperparathyroidism (Fig. 55-2). If the serum phosphorus concentration is increased and renal function is normal, hypervitaminosis D and bone osteolysis from metastatic or primary bone neoplasia are the primary differentials.

Determining whether renal failure is primary or secondary to hypercalcemia caused by another disorder when hyperphosphatemia and hypercalcemia co-exist with azotemia can be difficult. Chronic and, less commonly, acute renal failure can cause hypercalcemia. Alternatively, disorders that cause persistent hypercalcemia with a concurrent high-

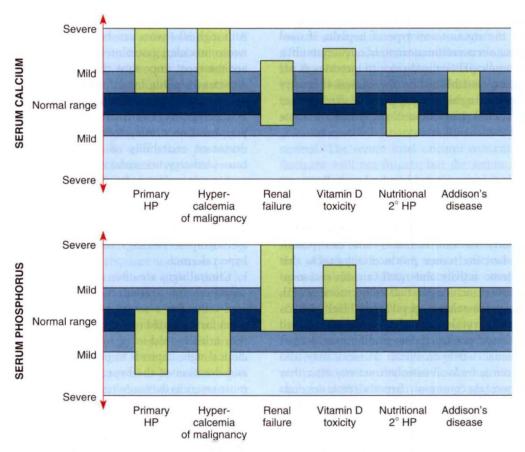


FIG 55-2
The range in serum calcium and phosphorus concentrations for the more common causes of hypercalcemia and/or hyperparathyroidism in the dog. HP, Hyperparathyroidism; 2° HP, secondary hyperparathyroidism. (From Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, ed 3, Philadelphia, 2004, WB Saunders.)

normal to increased serum phosphorus concentration can cause progressive mineralization of the kidney and eventual renal failure. Measurement of the serum ionized calcium concentration may help identify dogs and cats with renal failure—induced hypercalcemia; serum ionized calcium concentrations are typically normal or decreased in renal failure and increased in hypercalcemia caused by other disorders.

Hypercalcemia of malignancy and primary hyperparathyroidism are the primary differentials when hypercalcemia and normal-to-low serum phosphorus concentrations are identified. The most common malignancy is lymphoma. A careful review of the history and physical examination findings may provide clues to the diagnosis. Systemic signs of illness suggest hypercalcemia of malignancy. Dogs and cats with primary hyperparathyroidism are usually healthy, and clinical signs are mild. The appendicular skeleton, peripheral lymph nodes, abdominal cavity, and rectum should be carefully palpated for masses, lymphadenopathy, hepatomegaly, splenomegaly, or pain on digital palpation of the long bones. Diagnostic tests that are helpful in identifying the underlying malignancy include thoracic and abdominal radiographs; abdominal ultrasound; cytologic evaluation of aspirates of the liver, spleen, lymph nodes, and bone marrow; determination of the serum ionized calcium, PTH, and PTHrP concentrations; and cervical ultrasound.

Sternal and hilar lymphadenopathy is common with lymphoma-induced hypercalcemia and can be readily identified with thoracic radiographs. Radiographs of the thorax and abdomen can also be used to evaluate bones; discrete lytic lesions in the vertebrae or long bones suggest multiple myeloma. Hyperproteinemia, proteinuria, and plasma cell infiltration in the bone marrow suggest multiple myeloma. Cytologic evaluation of peripheral lymph node, bone marrow, and splenic aspirates can be helpful in identifying lymphoma; involvement of the peripheral lymph nodes or spleen by lymphoma can be present without causing their enlargement. Ideally, the largest lymph node should be evaluated. Normal lymph node, bone marrow, and splenic aspirates do not rule out lymphoma.

Measurement of the serum ionized calcium, PTH, and PTHrP levels from the same blood sample is helpful in differentiating primary hyperparathyroidism from HHM. Excessive secretion of biologically active PTHrP plays a central role in the pathogenesis of hypercalcemia in most forms of HHM. An increased serum ionized calcium concentration, a detectable serum PTHrP concentration, and a

nondetectable serum PTH concentration are diagnostic for HHM. Lymphoma is the most common cause of detectable PTHrP concentrations, but other tumors, including apocrine gland adenocarcinoma and various carcinomas (e.g., mammary gland, squamous cell, bronchogenic), can also cause hypercalcemia by this mechanism. In contrast, an increased serum ionized calcium concentration, a normal to increased serum PTH concentration, and a nondetectable PTHrP concentration are diagnostic of primary hyperparathyroidism. Ultrasonographic examination of the thyroparathyroid complex may reveal enlargement of one or more parathyroid glands. Most parathyroid adenomas measure 4 to 10 mm in greatest diameter, although parathyroid adenomas can exceed 2 cm. In contrast, the parathyroid glands will be small or undetectable with hypercalcemia of malignancy.

Evaluation of the change in the serum calcium concentration following L-asparaginase administration should be considered for the animal with hypercalcemia of undetermined etiology to rule out occult lymphoma. For the l-asparaginase trial 20,000 IU/m² of the drug is administered intravenously, and the serum calcium concentration is measured before and every 12 hours after administration for as long as 72 hours. A decline in the serum calcium level, usually into the normal range, is strongly suggestive of occult lymphoma. Hypersensitivity reactions are the most common adverse effect associated with l-asparaginase administration; pretreatment with an antihistamine is recommended.

Idiopathic hypercalcemia is a common diagnosis in young and middle-aged cats that is established by ruling out the other causes of hypercalcemia. Hypercalcemia is usually mild (less than 13 mg/dl), and cats are usually asymptomatic. The serum phosphorus concentration and renal parameters are normal. The etiology is unknown. The results of a complete diagnostic evaluation, as described previously, are unremarkable. Serum PTH concentrations are in the normal range or low; primary hyperparathyroidism has not been confirmed in any of these cats. Excessive serum PTHrP, 25hydroxyvitamin D or calcitriol concentrations have not been identified. Nephrocalcinosis and urolithiasis may develop, presumably secondary to increased urinary calcium excretion. Effective treatment has not been identified primarily because the pathogenesis of this problem remains unknown. Serum calcium concentrations have decreased in some cats after a change to a high-fiber diet or renal diets containing low calcium and phosphorus content or after prednisone treatment (initial dose, 5 mg q24h) was initiated, but the response has been unpredictable and often short-lived. Preliminary trials with oral biphosphonates (e.g., alendronate) have been promising in some cats with idiopathic hypercalcemia (see treatment section). Serum calcium, phosphorus, and renal parameters should be monitored periodically in affected cats and appropriate therapy initiated if renal insufficiency begins to develop (see Chapter 44).

#### **Treatment**

Medical therapy should be directed at eradicating the underlying cause of the hypercalcemia. Supportive therapy to



#### Nonspecific Therapy for Control of Hypercalcemia

#### **Acute Therapy**

- 1. Correct fluid deficits
- 2. Physiologic saline diuresis, 60-180 mg/kg/day IV
- 3. Furosemide, 2-4 mg/kg IV, IM, PO q8-12h
- Once diagnosis has been established: prednisone, 1-2 mg/kg q12h

#### Additional Therapy If Above Fails

- 1. Sodium bicarbonate, 1-4 mEq/kg given by slow bolus
- 2. Calcitonin, 4-8 IU/kg SC q8-12h
- 3. Bisphosphonates (pamidronate, 1-2 mg/kg IV)
- 4. Peritoneal dialysis, hemodialysis

#### Long-Term Therapy

- 1. Furosemide (see above)
- 2. Prednisone (see above)
- 3. Low-calcium diet (e.g., Prescription Diet k/d, u/d, s/d)
- Intestinal phosphate binders if hyperphosphatemia present (see Chapter 44)
- 5. Bisphosphonates (pamidronate (see above); etidronate, 10-40 mg/kg PO divided q8-12h)

IV, Intravenous; IM, intramuscular; PO, by mouth; SC, subcutaneous.

decrease the serum calcium concentration to less toxic levels is indicated if clinical signs are severe, if the serum calcium concentration is greater than 16 mg/dl, if the calcium-phosphorus solubility product ([Ca]  $\times$  [Pi]) is greater than 60 to 70 (implying metastatic mineralization of soft tissues), or if azotemia is present. In dogs and cats correction of fluid deficits, saline diuresis, diuretic therapy with furosemide, and corticosteroids are the most commonly used modes of therapy (Box 55-6). Prerenal azotemia is common in dogs with hypercalcemia secondary to water restriction imposed by owners concerned about the polyuria and polydipsia. As such, diuretics should never be administered before volume replenishment is completed.

The supportive therapy implemented should not interfere with attempts to establish a definitive diagnosis. As a general rule, saline diuresis followed by diuretic therapy can be initiated without compromising the results of diagnostic tests. Because of the high incidence of lymphoma in animals with hypercalcemia, glucocorticoids should not be administered unless the cause of the hypercalcemia has been identified.

Calcitonin may be useful in the treatment of animals with severe hypercalcemia and could be used in lieu of prednisone for treating hypercalcemia in animals without a definitive diagnosis. Calcitonin inhibits osteoclast activity. It has been used most commonly to treat hypercalcemia in dogs with cholecalciferol rodenticide toxicosis. The decrease in the serum total calcium concentration after calcitonin administration is relatively small (3 mg/dl or less), and adverse reactions include anorexia and vomiting. Although the onset of

action of calcitonin may be rapid, its effect may be short-lived (hours), and resistance often develops within a few days, presumably because of downregulation of calcitonin receptors. The transitory effect of calcitonin and its expense have limited its usefulness for treating hypercalcemia.

Bisphosphonates inhibit bone resorption by decreasing osteoclast activity and function and inducing osteoclast apoptosis and are used for maintenance treatment of hypercalcemia of malignancy, osteoporosis, and malignancyinduced bone pain in humans. Pamidronate (Aredia, Novartis) has been used to treat dogs and cats with a variety of disorders causing hypercalcemia, including cholecalciferol rodenticide toxicosis, hypercalcemia caused by lymphoma, myeloma, primary hyperparathyroidism, and nocardiosis. The IV administration of pamidronate has a rapid onset of action and is effective in lowering serum total and ionized calcium concentrations. The only adverse reaction reported with pamidronate is renal toxicity, which appears to be uncommon. Factors that affect onset of renal toxicity in humans include type of bisphosphonate administered, rate of infusion, and hydration status of the patient. Administration of pamidronate before a definitive diagnosis has been obtained should not adversely affect establishing the cause of the hypercalcemia. Unfortunately, expense limits the usefulness of pamidronate for treating hypercalcemia in animals. The reader is referred to Suggested Readings for more information on bisphosphonates.

The duration of therapy for hypercalcemia depends on the reversibility of the underlying cause. If prolonged supportive therapy is required (e.g., in an animal with cholecal-ciferol rodenticide toxicity or nontreatable malignancy), furosemide, corticosteroids, and a low-calcium diet (e.g., Prescription Diets u/d and s/d canned, Hill's Pet Products) can be used to help control the hypercalcemia. Noncalcium-containing intestinal phosphorus binders (e.g., aluminum hydroxide) should be administered if hyperphosphatemia is present. Oral or IV administration of bisphosphonates, as needed to control hypercalcemia, may also be considered (see Suggested Readings).

#### HYPOCALCEMIA

#### Etiology

Hypocalcemia is present if the serum total calcium concentration is less than 9 mg/dl in adult dogs and less than 8 mg/dl in adult cats or if the serum ionized calcium concentration is less than 1.0 mmol/L, although reference ranges may vary between laboratories. Hypocalcemia develops after increased calcium loss in milk (e.g., puerperal tetany), decreased calcium resorption from bone or kidney (e.g., primary hypoparathyroidism), decreased calcium absorption from the gastrointestinal tract (e.g., malassimilation syndromes), or increased precipitation-chelation of serum calcium (e.g., ethylene glycol toxicity, acute pancreatitis). The acute onset of hyperphosphatemia can also cause hypocalcemia. The most common causes of hypocalcemia in dogs and cats are

puerperal tetany, acute and chronic renal failure, malassimilation syndromes, and primary hypoparathyroidism (especially after thyroidectomy in hyperthyroid cats; see Table 50-3). The serum total calcium concentration is typically decreased in animals with concurrent hypoalbuminemia for reasons discussed in the section on hypercalcemia. Depending on the underlying etiology, the serum ionized calcium concentration may or may not be decreased. Measurement of serum ionized calcium should be done before rendering a diagnosis of hypocalcemia in an animal with decreased serum total calcium and albumin concentrations.

#### **Clinical Features**

Animals with hypocalcemia range from being asymptomatic to showing severe neuromuscular dysfunction. Serum total calcium concentrations between 7.5 and 9 mg/dl are often clinically silent; clinical signs usually occur if values are less than 7 mg/dl. The presence and severity of signs depend on the magnitude, rapidity of onset, and duration of hypocalcemia.

The most common clinical signs are directly attributable to a hypocalcemia-induced increase in neuronal excitability and include nervousness, behavioral changes, focal muscle twitching (especially ear and facial muscles), muscle cramping, stiff gait, tetany, and seizures. The seizures are not usually associated with loss of consciousness or urinary incontinence. Early indicators of hypocalcemia, especially in cats, include lethargy, anorexia, intense facial rubbing, and panting. Exercise, excitement, and stress may induce or worsen clinical signs. Additional physical examination findings may include fever, a "splinted" abdomen, cardiac abnormalities (e.g., weak femoral pulses, muffled heart sounds, tachyarrhythmias), and cataracts.

#### Diagnosis

Hypocalcemia should be confirmed before initiating diagnostic tests to identify the cause. The list of differential diagnoses for hypocalcemia is relatively short, and the history, physical examination findings, CBC, serum biochemistry panel, urinalysis, and tests for pancreatitis (e.g., pancreatic lipase immunoreactivity, abdominal ultrasound) usually provide the clues necessary to establish the diagnosis (see Table 50-3). Primary hypoparathyroidism is the most likely diagnosis in the nonazotemic, nonlactating dog or cat with clinical signs of hypocalcemia. The finding of a low or non-detectable baseline serum PTH concentration confirms this diagnosis.

#### **Treatment**

Therapy should be directed at eradicating the underlying cause of the hypocalcemia. Vitamin D, calcium, or both are indicated if clinical signs of hypocalcemia are present, if the serum calcium concentration is less than 7.5 mg/dl, or if the serum ionized calcium concentration is less than 0.8 mmol/L. If hypocalcemic tetany is present, calcium should be administered intravenously slowly to effect (Box 55-7). Calcium gluconate is the preferred agent because it is not



# Treatment Of Hypocalcemia in Dogs and Cats

#### **Immediate Treatment of Symptomatic Hypocalcemia**

Calcium gluconate (preferred) or calcium chloride 10% solution

Dosage: 0.5-1.5 ml/kg IV slowly to effect Monitor for bradycardia and arrythmias Goal: Resolve clinical signs of hypocalcemia

### Parenteral Treatment to Prevent Symptomatic Hypocalcemia

Continuous IV infusion of 10% calcium gluconate (preferred)

Initial dosage: 60 to 90 mg elemental calcium/kg/day 10 ml of 10% calcium gluconate provides 93 mg of elemental calcium

Administer via syringe pump in separate IV line

Do not add to fluids containing lactate, acetate, bicarbonate or phosphates

Monitor serum ionized or total calcium q8-12h, and adjust infusion rate accordingly

Goal: to avoid clinical signs of hypocalcemia while correcting etiology and/or waiting for oral calcium and vitamin D therapy to take effect

Periodic SC administration of calcium gluconate

Dilute 10% calcium gluconate at least 1:2 with physiologic saline before administration

Do not administer calcium chloride subcutaneously; sloughing of skin may occur

Dosage based on amount of IV calcium required to control clinical signs during treatment of symptomatic hypocalcemia (see above)

Administer q6-8h

Monitor serum ionized or total calcium prior to injection and adjust dosage or frequency of administration accordingly

Goal: to avoid clinical signs of hypocalcemia while correcting etiology and/or waiting for oral calcium and vitamin D therapy to take effect

#### Oral Vitamin D and Calcium Treatment for Hypocalcemia

1,25-dihydroxy vitamin  $D_3$  (calcitriol) is preferred because of its fast onset of action

Available as 0.25-µg capsules

Initial dosage: 0.02-0.03 µg/kg/day (compounding of drug often required)

Monitor serum ionized or total calcium q12-24h, and adjust dosage or frequency of administration accordingly

Goal: to avoid clinical signs of hypocalemia and development of hypercalcemia; target total calcium concentration is between 9 and 10 mg/dl

Dihydrotachysterol (Hytakerol) has a slower onset of action compared with calcitriol

Available as 0.125-mg tablets and capsules and 0.25 mg/ml oral solution

Initial dosage: 0.02-0.03 mg/kg/day

Monitor serum ionized or total calcium q12-24h and adjust dosage or frequency of administration accordingly

Goal: to avoid clinical signs of hypocalemia and development of hypercalcemia; target total calcium concentration is between 9 and 10 mg/dl

Oral calcium gluconate, calcium lactate, or calcium carbonate tablets

Various tablet strengths available, ranging from 30 to 500 mg of calcium/tablet

Initial dosage: approximately 25 mg of Ca/kg q8-12h

Typically used in conjunction with vitamin D

Dosage and frequency of administration adjusted on the basis of serum ionized or total calcium concentrations

IV, Intravenous; SC, subcutaneous.

caustic if administered outside of the vein, unlike calcium chloride. Auscultation and electrocardiographic monitoring is advisable during calcium administration; if bradycardia or shortening of the QT interval occurs, the IV infusion should be stopped briefly. Calcium-rich fluids should be infused with caution in dogs or cats with hyperphosphatemia because they can increase the probability of metastatic calcification of soft tissues, most notably in the kidney.

Once signs of hypocalcemic tetany have been controlled with IV calcium, oral vitamin D, oral or injectable calcium (or both) may be needed to prevent the recurrence of clinical signs. If the cause of hypocalcemia is readily reversible and the hypocalcemia is anticipated to be short-lived (e.g., weaning puppies from bitch with puerperal tetany), an injection of calcium gluconate subcutaneously may be all that is necessary to prevent the recurrence of clinical signs. The clinician can determine the dose of IV calcium gluconate required to control tetany originally, and this dose can then

be administered subcutaneously after the calcium gluconate has been diluted at least 1:2 by volume with saline. Calcium chloride should never be administered subcutaneously because it is highly irritating to tissues and may cause sluffing of the skin.

In animals with disorders causing prolonged hypocalcemia (e.g., primary hypoparathyroidism), calcium gluconate should be administered by continuous IV infusion at an initial dosage of 60 to 90 mg of elemental calcium/kg/day. Ten milliliters of 10% calcium gluconate provides 93 mg of elemental calcium. Approximately 1, 2, and 3 mg/kg/hour elemental calcium is provided when 10, 20, or 30 ml of 10% calcium gluconate, respectively, is added to 250 ml of fluids and administered at a maintenance rate of 60 ml/kg/day (2.5 ml/kg/hour). Calcium salts should not be added to fluids that contain lactate, acetate, bicarbonate, or phosphates because calcium salt precipitates can result. The serum calcium concentration should be measured daily and

calcium therapy gradually decreased and then discontinued once the serum total calcium concentration is consistently greater than 8 mg/dl or the serum ionized calcium concentration is greater than 0.9 mmol/L.

Long-term maintenance therapy may be necessary to control hypocalcemia. It is most commonly required for the control of primary hypoparathyroidism and hypoparathyroidism occurring after bilateral thyroidectomy in cats with hyperthyroidism. Oral vitamin D administration is the primary mode of treatment for the management of chronic hypocalcemia (see Box 55-7). Vitamin D works by stimulating intestinal calcium and phosphorus absorption and, together with parathyroid hormone, by mobilizing calcium and phosphorus from bone. Oral calcium supplements are needed early in maintenance therapy in addition to vitamin D.

The aim of maintenance therapy is to keep the serum calcium concentration between 9 and 10 mg/dl, which controls clinical signs, lessens the risk of hypercalcemia, and provides some stimulus for remaining or ectopic parathyroid tissue to become functional. The serum calcium concentration should be monitored closely (initially q24-48h) and adjustments in therapy made accordingly. Vitamin D therapy is required permanently in animals with primary hypoparathyroidism and in animals that have undergone total parathyroidectomy. Vitamin D therapy can usually be tapered and discontinued if there is only partial or transient parathyroid damage. Regardless, calcium supplementation often may be tapered and stopped. See Chapter 50 for more information on the treatment of hypocalcemia.

# **HYPERPHOSPHATEMIA**

#### Etiology

Hyperphosphatemia is present when the serum phosphorus concentration is greater than 6.5 mg/dl in the adult dog and cat, although reference ranges may vary between laboratories. Serum phosphorus concentrations are highest (often greater than 6.5 mg/dl) in dogs and cats younger than 6 months of age and gradually decrease to adult values after 1 year of age. Bone growth and an increase in renal tubular reabsorption of phosphorus mediated by growth hormone are believed to contribute to this age effect. Hyperphosphatemia can result from increased intestinal phosphorus absorption, decreased phosphorus excretion in the urine, or a shift in phosphorus from the intracellular to the extracellular compartment. Translocation of phosphorus between the intracellular and extracellular compartment is similar to that of potassium. The most common cause of hyperphosphatemia in dogs and cats is decreased renal excretion secondary to renal failure (Box 55-8).

### **Clinical Features**

Hyperphosphatemia is a marker of underlying disease. By itself, hyperphosphatemia usually does not cause clinical signs. An acute increase in serum phosphorus may cause



Causes of Hyperphosphatemia in Dogs and Cats

#### **Physiologic**

Young growing animal\*

#### Increased Input

Hypervitaminosis D\*
Excess supplementation
Cholecalciferol rodenticides
Jasmine toxicity
Excess dietary intake
Osteolytic bone lesions (neoplasia)

#### **Decreased Loss**

Acute or chronic renal failure\* Hypoparathyroidism\* Hyperthyroidism Hyperadrenocorticism Acromegaly

# Transcellular Shifts (ICF to ECF)

Metabolic acidosis Tumor cell lysis syndrome Tissue trauma or rhabdomyolysis Hemolysis

#### latrogenic

IV phosphorus administration Phosphate-containing enemas Diuretics: furosemide and hydrochlorothiazides

# **Laboratory Error**

Lipemia Hyperproteinemia

Modified from DiBartola SD, Willard MD: Disorders of phosphorus: hypophosphatemia and hyperphosphatemia. In DiBartola SP, editor: Fluid, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders Elsevier.

ICF, Intracellular fluid; ECF, extracellular fluid; IV, intravenous. \*Common causes.

hypocalcemia and its associated neuromuscular signs. Sustained hyperphosphatemia can cause secondary hyperparathyroidism, fibrous osteodystrophy, and metastatic calcification in extraosseous sites. Fortunately, most causes of hyperphosphatemia cause a decrease in serum calcium concentration so that the calcium-phosphorus solubility product ([Ca]  $\times$  [Pi]) remains less than 60. The risk of soft tissue mineralization increases when the [Ca]  $\times$  [Pi] solubility product exceeds 60 to 70. Chronic renal failure is the most common cause of sustained hyperphosphatemia and an increase in the solubility product above 60 to 70.

#### **Treatment**

Hyperphosphatemia usually resolves with correction of the underlying disease. In dogs and cats with renal failure, hyperphosphatemia can initially be lowered with aggressive fluid therapy. Low-phosphorus diets and orally administered phosphate binders are the most effective way to treat sustained hyperphosphatemia caused by renal failure (see Chapter 44).

### **HYPOPHOSPHATEMIA**

# **Etiology**

Hypophosphatemia is present when the serum phosphorus concentration is less than 3 mg/dl in the dog and cat, although reference ranges may vary between laboratories. Hypophosphatemia is usually not clinically worrisome until the serum phosphorus concentration is less than 1.5 mg/dl. Hypophosphatemia results from decreased phosphorus absorption in the intestinal tract, increased urinary phosphorus excretion, or translocation from the extracellular to the intracellular compartment. The most common cause of clinically significant hypophosphatemia in the dog and cat occurs within the first 24 hours of therapy for diabetic ketoacidosis, when there is a shift of potassium and phosphorus from the extracellular to the intracellular compartment (Box 55-9). Translocation of phosphorus between the intracellular and



BOX 55-9

Causes of Hypophosphatemia in Dogs and Cats

### **Decreased Intestinal Absorption**

Phosphate binders\*
Vitamin D deficiency
Decreased dietary intake (?)
Malabsorption, steatorrhea (?)

# **Increased Urinary Excretion**

Primary hyperparathyroidism\*
Humoral hypercalcemia of malignancy\*
DKA\*
Renal tubular disorders (Fanconi syndrome)
Proximally acting diuretics
Eclampsia

#### Transcellular Shifts

Insulin administration, especially for DKA\*
Respiratory and metabolic alkalosis
Sodium bicarbonate administration\*
Parenteral glucose administration\*
Parenteral nutritional solutions
Hypothermia

#### Laboratory Error

Modified from DiBartola SD, Willard MD: Disorders of phosphorus: hypophosphatemia and hyperphosphatemia. In DiBartola SP, editor: Fluid, electrolyte and acid-base disorders in small animal practice, ed 3, St Louis, 2006, Saunders Elsevier.

DKA, Diabetic ketoacidosis.

extracellular compartments is similar to that seen with potassium. Factors that promote a shift of potassium into the intracellular compartment (e.g., alkalosis, insulin, glucose infusion) promote a similar shift in phosphorus. During therapy for diabetic ketoacidosis the serum phosphorus concentration can decline to severe levels (i.e., less than 1 mg/dl) as a result of the dilutional effects of fluid therapy and the intracellular shift of phosphorus after the initiation of insulin and bicarbonate therapy. Interestingly, the initial serum phosphorus concentration is usually normal or only mildly decreased because the metabolic acidosis of diabetic ketoacidosis results in a shift of phosphorus from the intracellular to the extracellular compartment.

#### **Clinical Features**

Clinical signs may develop when the serum phosphorus concentration is less than 1.5 mg/dl, although signs are quite variable, and severe hypophosphatemia is clinically silent in many animals. Hypophosphatemia primarily affects the hematologic and neuromuscular systems in the dog and cat. Hemolytic anemia is the most common sequela to hypophosphatemia. Hypophosphatemia decreases the erythrocyte concentration of ATP, which increases erythrocyte fragility, leading to hemolysis. Hemolysis is usually not identified until the serum phosphorus concentration is 1 mg/dl or less. Hemolytic anemia can be life-threatening if not recognized and treated. Neuromuscular signs include weakness, ataxia, and seizures, as well as anorexia and vomiting secondary to intestinal ileus.

# **Treatment**

For most dogs and cats hypophosphatemia resolves after correction of the underlying cause. Phosphate therapy is probably not indicated for asymptomatic animals in which the serum phosphorus concentration is greater than 1.5 mg/dl and is unlikely to decrease further. Phosphate therapy is indicated if clinical signs or hemolysis are identified or if the serum phosphorus concentration is less than 1.5 mg/dl, especially if a further decrease is possible. Phosphate supplementation is not indicated in dogs and cats with hypercalcemia, hyperphosphatemia, oliguria, or suspected tissue necrosis. If renal function is in question, phosphorus supplementation should not be done until the status of renal function and serum phosphorus concentration are known.

The goal of therapy is to maintain the serum phosphorus concentration greater than 2 mg/dl without causing hyperphosphatemia. Oral phosphate supplementation is preferred, using a buffered laxative (e.g., Phospho-Soda, Fleet Pharmaceuticals), balanced commercial diets, milk, or a combination of these. IV phosphate supplementation is usually required to correct severe hypophosphatemia, especially in animals with diabetic ketoacidosis. Potassium phosphate solutions are typically used. If potassium supplementation is contraindicated, sodium phosphate solutions can be substituted. Potassium and sodium phosphate solutions contain 3 mmol of phosphate per milliliter and either 4.4 mEq of potassium or 4 mEq of sodium per milliliter. The initial

<sup>\*</sup>Common causes.

dosage of phosphate is 0.01 to 0.03 mmol/kg/hour, preferably administered by constant rate infusion in calcium-free IV fluids (i.e., 0.9% sodium chloride). In dogs and cats with severe hypophosphatemia, it may be necessary to increase the dosage to 0.03 to 0.12 mmol/kg/hour. Because the dose of phosphate necessary to replete an animal and the animal's response to therapy cannot be predicted, it is important to initially monitor the serum phosphorus concentration every 8 to 12 hours and adjust the phosphate infusion accordingly. Adverse effects from overzealous phosphate administration include iatrogenic hypocalcemia and its associated neuromuscular signs, hypernatremia, hypotension, and metastatic calcification. Serum total or preferably ionized calcium concentration should be measured at the same time as serum phosphorus concentration and the rate of phosphate infusion decreased if hypocalcemia is identified.

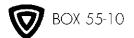
# HYPOMAGNESEMIA

# Etiology

Hypomagnesemia is present if the serum total and ionized magnesium concentration are less than 1.5 mg/dl and 1.0 mg/dl, respectively, although reference ranges may vary between laboratories. Hypomagnesemia results from decreased oral intake or gastrointestinal tract absorption of magnesium (e.g., small intestinal disease causing malabsorption), increased gastrointestinal tract loss (e.g., protracted vomiting, diarrhea), increased urinary magnesium excretion (e.g., interstitial nephritis, diuretics), or translocation of the cation from the extracellular to the intracellular compartment. The most common causes of clinically significant hypomagnesemia in dogs and cats include disorders causing small intestinal malassimilation; renal disorders associated with a high urine output; the osmotic diuresis of diabetic ketoacidosis; and the shift of potassium, phosphorus, and magnesium from the extracellular to the intracellular compartment that occurs within the first 24 hours of therapy for diabetic ketoacidosis (Box 55-10). Magnesium is predominantly an intracellular cation. The nature of the translocation of magnesium between the intracellular and the extracellular compartments is similar to that of potassium in that factors that promote a shift of potassium into the intracellular compartment (e.g., alkalosis, insulin, glucose infusion) promote a similar shift in magnesium.

# **Clinical Features**

Hypomagnesemia is reported to be the most common electrolyte disorder in critically ill dogs and cats, and magnesium deficiency may predispose animals to a variety of cardiovascular, neuromuscular, and metabolic complications. Clinical signs of hypomagnesemia do not usually occur until the serum total and ionized magnesium concentrations are less than 1.0 mg/dl and 0.5 mg/dl, respectively, and even at these low levels, many animals remain asymptomatic. A magnesium deficiency can result in several nonspecific clinical signs, including lethargy, anorexia, muscle weakness (includ-



Causes of Hypomagnesemia and Magnesium Depletion in Dogs and Cats

#### **Gastrointestinal Causes**

Inadequate intake
Chronic diarrhea and vomiting\*
Malabsorption syndromes
Acute pancreatitis
Cholestatic liver disease
Nasogastric suction

#### **Renal Causes**

Renal failure
Renal tubular acidosis
Postobstructive diuresis
Drug-induced tubular injury (e.g., aminoglycosides, cisplatin)
Post renal transplant
Prolonged intravenous fluid therapy\*
Diuretics\*
Digitalis administration
Concurrent electrolyte disorders
Hypercalcemia

#### **Endocrine Causes**

Hypokalemia

Hypophosphatemia

Diabetes mellitus and diabetic ketoacidosis\* Hyperthyroidism Primary hyperparathyroidism Primary hyperaldosteronism

#### Miscellaneous Causes

Acute administration of insulin, glucose, or amino acids Sepsis Hypothermia Massive blood transfusion Peritoneal dialysis, hemodialysis Total parenteral nutrition

Modified from Bateman S: Disorders of magnesium: magnesium deficit and excess. In DiBartola SP, editor: *Fluid, electrolyte and acid-base disorders in small animal practice,* ed 3, St Louis, 2006, Saunders/Elsevier.

\*Common causes.

ing dysphagia and dyspnea), muscle fasciculations, seizures, ataxia, and coma. Concurrent hypokalemia, hyponatremia, and hypocalcemia occur in animals with hypomagnesemia, although the prevalence of these electrolyte abnormalities may differ between species. These electrolyte abnormalities may also contribute to the development of clinical signs. Magnesium is a cofactor for all enzyme reactions that involve ATP, most notably the sodium-potassium ATPase pump. Deficiencies in magnesium can lead to potassium wastage from the body, and the resultant hypokalemia may be refractory to appropriate potassium replacement therapy.

Magnesium deficiency inhibits PTH secretion from the parathyroid gland, resulting in hypocalcemia. Magnesium deficiency causes the resting membrane potential of myocardial cells to be decreased and leads to increased Purkinje fiber excitability, with the consequent generation of arrhythmias. Electrocardiographic changes include a prolonged PR interval, widened QRS complex, depressed ST segment, and peaked T waves. Cardiac arrhythmias associated with magnesium deficiency include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation. Hypomagnesemia also predisposes animals to digitalis-induced arrhythmias.

# Diagnosis

Measurement of serum total and ionized magnesium is indicated in those dogs and cats with disorders and predisposing factors that are associated with hypomagnesemia (see Box 55-10). Assessing an animal's magnesium status is problematic, however, because there is no simple, rapid, and accurate laboratory test to gauge total body magnesium status. Serum total magnesium represents 1% of the body's magnesium stores, and serum ionized magnesium represents 0.2% to 0.3% of total body magnesium stores. As a result, serum total and ionized magnesium concentrations do not always reflect total body magnesium status. A normal serum magnesium concentration may exist despite an intracellular magnesium deficiency. However, a low serum magnesium concentration would support the presence of a total body magnesium deficiency, especially when clinical signs or concurrent electrolyte abnormalities are consistent with hypomagnesemia.

#### **Treatment**

To date there are no clinical studies that have yielded guidelines for magnesium replacement in dogs and cats; currently, it is determined empirically. Hypomagnesemia is not generally a concern for dogs and cats eating commercial diets. Treatment of hypomagnesemia usually involves sick dogs and cats that are hospitalized and have problems with inappetence and/or excessive fluid loss from the gastrointestinal tract or kidneys. Treatment of hypomagnesemia may also be indicated during treatment of diabetic ketoacidosis in dogs and cats with refractory hypokalemia, hypocalcemia, or both and in dogs or cats in heart failure with concurrent ventricular arrhythmias that are being treated with loop diuretics, digitalis, or both.

Parenteral solutions of magnesium sulfate (8.12 mEq of magnesium per gram of salt) and magnesium chloride (9.25 mEq of magnesium per gram of salt) are available commercially. The IV dose for rapid and slow magnesium replacement is 0.75 to 1 mEq/kg/day and 0.3 to 0.5 mEq/kg/day, respectively, administered by constant-rate infusion in 5% dextrose in water. Magnesium is incompatible with solutions containing bicarbonate or calcium. Renal function should be assessed before the administration of magnesium and the magnesium dose reduced by 50% to 75% in azotemic animals. The use of magnesium with digitalis cardio-

glycosides may cause serious conduction disturbances. Serum magnesium, calcium, and potassium concentrations should be monitored daily. The goal of magnesium therapy is the resolution of clinical signs or refractory hypokalemia and hypocalcemia. The parenteral administration of magnesium sulfate may cause significant hypocalcemia such that calcium infusion may be necessary. Other adverse effects of magnesium therapy include hypotension; atrioventricular and bundle-branch blocks; and, in the event of overdose, respiratory depression and cardiac arrest. Overdoses are treated with IV calcium gluconate (see Box 55-7).

# HYPERMAGNESEMIA

# Etiology

Hypermagnesemia is present if the serum total and ionized magnesium concentration is greater than 2.5 mg/dl and 1.5 mg/dl, respectively, although reference ranges may vary between laboratories. It is an uncommon clinical problem, owing to the remarkable ability of the kidney to efficiently eliminate excessive magnesium. Hypermagnesemia may occur in dogs and cats with renal failure and postrenal azotemia and iatrogenically after an excessive intake of magnesium (e.g., IV administration). Because excess magnesium is rapidly excreted by the healthy kidney, iatrogenic hypermagnesemia usually occurs in animals with renal insufficiency. Hypermagnesemia has also been reported in cats with thoracic neoplasia and pleural effusion, although the mechanism involved with the development of hypermagnesemia in these cats is unknown.

# **Clinical Features**

Clinical manifestations of hypermagnesemia include lethargy, weakness, and hypotension. Loss of deep tendon reflexes and electrocardiographic changes, consisting of prolonged PR intervals, widening QRS complexes, and heart block, occur at higher serum magnesium concentrations. Serious complications, including respiratory depression, apnea, cardiac arrhythmias, and cardiac arrest, occur when serum magnesium concentrations exceed 12 mg/dl. At these high levels magnesium acts as a nonspecific calcium-channel blocker.

# **Diagnosis**

Measurement of the serum magnesium concentration identifies hypermagnesemia. Unlike magnesium depletion, serum concentrations cannot be normal if there is an increase in magnesium stores (see the section on hypomagnesemia). A correlation between increased serum magnesium concentrations and the severity of total body excess has not been reported.

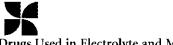
### **Treatment**

Treatment begins with the discontinuation of all exogenous sources of magnesium. Additional treatment depends on the severity of the hypermagnesemia, the clinical presentation, and the status of renal function. Most dogs and cats with healthy kidneys require only supportive care and observation. Treatment aimed at improving renal function is indicated in animals with concurrent renal insufficiency (see Chapter 44). Saline diuresis and administration of loop diuretics (e.g., furosemide) will accelerate renal magnesium excretion. Administration of IV calcium is indicated in dogs and cats with cardiac arrhythmias or significant hypotension (see Box 55-7).

# Suggested Readings

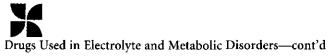
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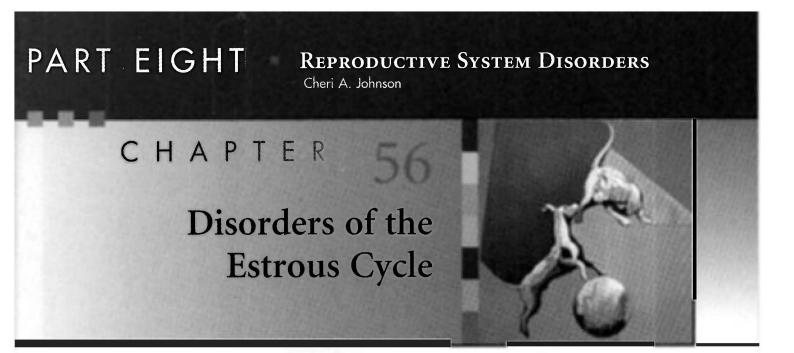
Drugs Used in Electrolyte and Metabolic Disorders

GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Calcitonin — salmon (Calcimar)	Treat hypercalcemia	4-8 U/kg SC q8-12h	Unknown
Calcium—injectable and oral preparations	Treat hypocalcemia	See Box 55-7	See Box 55-7
Calcium gluconate 10%	Treat hyperkalemia	2-10 ml IV, slow bolus; 0.5-1.0 ml/kg IV, slow bolus	1-5 ml IV, slow bolus; 0.5-1.0 ml/kg IV, slow bolus
Cholestyramine (Questran)	Treat idiopathic hypercholesterolemia	1-2 g PO q12h	Unknown
Clofibrate (Átromid-S)	Treat idiopathic hypertriglyceridemia	500 mg PO q12h	Unknown
Dirlotapide (Slentrol)	Treat obesity	Initial dose: 0.01 ml/kg PO q12h × 14 days, then 0.02 ml/kg PO q12h × 14 days, then adjust accordingly	Do not use in cats
Etidronate disodium (Didronel)	Treat hypercalcemia	10-40 mg/kg PO divided q8-12h	10-40 mg/kg PO divided q8-12h
Furosemide (Lasix)	Treat hypercalcemia and hypermagnesemia	2-4 mg/kg PO, IV q8-12h	2-4 mg/kg PO, IV q8-12h
Gemfibrozil (Lopid)	Treat idiopathic hypertriglyceridemia	200 mg PO q24h	10 mg/kg PO q12h



GENERIC NAME (TRADE NAME)	PURPOSE	RECOMMENDED DOSE	
		DOG	CAT
Insulin — regular crystalline	Treat hyperkalemia	0.5-1.0 U/kg plus 2 g dextrose/U of insulin in parenteral fluids IV	0.5-1.0 U/kg plus 2 g dextrose/U of insulin in parenteral fluids IV
Lovastatin (Mevacor)	Treat idiopathic hypercholesterolemia	10-20 mg PO q24h	Unknown
Magnesium—injectable and oral preparations	Treat hypomagnesemia	See p. 881	See p. 881
Fish oil supplements rich in omega-3 fatty acids	Treat idiopathic hypertriglyceridemia	200-220 mg/kg PO q24h	Unknown
Niacin	Treat idiopathic hypertriglyceridemia	100 mg PO q24h	Unknown
Pamidronate (Aredia)	Treat hypercalcemia	1-2 mg/kg IV	1-2 mg/kg IV
Potassium gluconate (Kaon Elixir, Tumil-K)	Treat hypokalemia	2.2 mEq K/100 kcal food consumed per day or 2 mEq K/4.5 kg PO q 2h	2.2 mEq K/100 kcal food consumed per day or 2 mEq K/4.5 kg PO q12h
Prednisone (dog), Prednisolone (cat)	Treat hypercalcemia	1-2 mg/kg PO q12h	1-2 mg/kg PO q12h
Sodium bicarbonate Vitamin D preparations	Treat hyperkalemia Treat hypocalcemia	1-2 mEq/kg IV, slow bolus See Box <i>55-7</i>	1-2 mEq/kg IV, slow bolus See Box 55-7

SC, Subcutaneous; IV, intravenous; PO, oral.



# CHAPTER OUTLINE

#### NORMAL ESTROUS CYCLE

The Bitch

The Queen

# DIAGNOSTIC TESTS FOR THE REPRODUCTIVE TRACT

Vaginal Cytology

Vaginoscopy

Vaginal Bacterial Cultures

Virology

Assessment of Reproductive Hormones

Diagnostic Imaging

Karyotyping

Laparoscopy and Celiotomy

# FEMALE INFERTILITY

Failure to Cycle

Prolonged Interestrous Interval

Short Interestrous Interval

Abnormal Proestrus and Estrus

Normal Cycles

# ESTRUS SUPPRESSION, CONTRACEPTION, AND POPULATION CONTROL

Surgical Methods

Nonsurgical Methods for Contraception or

Sterilization

Contraception

# OVARIAN REMNANT SYNDROME

OVARIAN NEOPLASIA

ESTRUS AND OVULATION INDUCTION

The Queen

The Bitch

# NORMAL ESTROUS CYCLE

# THE BITCH

The average age at the time of puberty in bitches is 9 to 10 months, and the range is 6 to 24 months of age. The interval from the beginning of one cycle to the beginning of the next, or the interestrous interval, varies from 4 to 12 months and averages 7 months. Therefore bitches have only one or two cycles per year. The interestrous interval is extremely variable within individual bitches, more so than it is among bitches. Because of this variability, the past interestrous interval does not accurately predict the next cycle in an individual bitch. Although a few bitches are very consistent, in most there is more than a month's variation from cycle to cycle. The interestrous interval is not influenced by pregnancy or the photoperiod, although breeds such as the Basenji cycle only once each year, indicating a possible effect of the photoperiod in some individuals.

The estrous cycle in the bitch is divided into four components: proestrus, estrus, diestrus, and anestrus. Proestrus and estrus together are often referred to as *heat* or *season*. Together they constitute the follicular phase of the reproductive cycle. The luteal phase of the cycle is referred to as *diestrus*. The canine estrous cycle is distinctly different from that of other domestic species in several regards. These include the very long anestrus (months as opposed to days or weeks), the long proestrus and estrus (days to weeks as opposed to hours or days), the fact that the corpora luteal lifespan is independent of the presence (or absence) of pregnancy, ovulation of an immature oocyte, and long viability (days as opposed to hours) of oocyte and sperm within the female tract.

#### **Proestrus**

Proestrus is considered to begin when vulvar swelling and a sanguineous discharge are first observed. It ends when the bitch allows copulation. The average duration of proestrus is 9 days, and the range is 3 to 17 days. Attractiveness and

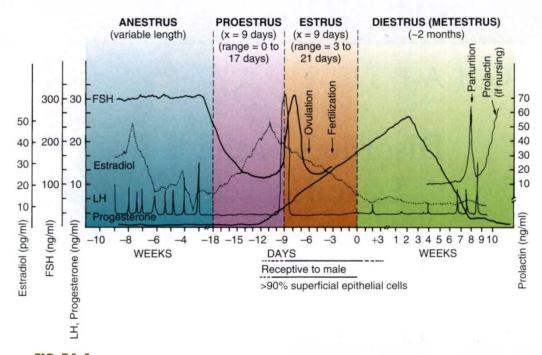


FIG 56-1 The canine estrous cycle. (From Morrow DA, editor: Current therapy in theriogenology, ed 2, Philadelphia, 1986, WB Saunders.)

receptivity to male dogs gradually increase throughout proestrus. The factors that end anestrus and initiate a new follicular phase in the bitch are poorly understood. Throughout anestrus follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are secreted concomitantly, in a pulsatile pattern. The FSH pulses are of lesser magnitude but longer duration than are the LH pulses. Basal concentrations of FSH increase as anestrus progresses, whereas basal LH concentrations are unchanged. The increase in FSH concentrations is considered crucial to initiate ovarian follicular development and the onset of proestrus. The developing ovarian follicles are 1.5 to 5 mm in diameter. They produce estrogens, the most important of which is estradiol 17-1. Estradiol causes the vulvar swelling, vaginal edema and cornification, and uterine bleeding that is recognized by a serosanguineous vulvar discharge. Estradiol serum concentrations gradually increase during early proestrus. They increase sharply just before the preovulatory LH surge and rapidly decline to basal levels thereafter (Fig. 56-1).

Under the influence of estrogen the vaginal epithelial cells proliferate and mature (cornification). The stratified squamous epithelium increases in thickness from a few cell layers in anestrus to 20 to 30 cell layers in late proestrus. The degree of estrogenic influence and therefore the stage of the estrous cycle with respect to the serum estrogen concentration can be monitored by vaginal cytology (see p. 891).

#### Estrus

Behavioral estrus is characterized by acceptance of mating. The bitch's feet are firmly planted to allow the male to mount—hence the term standing heat (Fig. 56-2). The tail is

deviated to the side to allow intromission; this behavior has been referred to as flagging. Stroking the perineum may occasionally elicit flagging, which would be an indication that the bitch is in estrus. The average duration of estrus is 9 days, and the range is 3 to 21 days. The swollen vulva is less turgid than during proestrus. The vulvar discharge of estrus is usually less bloody than that of proestrus, but normal bitches often have a sanguineous discharge throughout both. Therefore changes in the gross appearance of the discharge are not necessarily indicators of the transition from proestrus to estrus.

The preovulatory follicles have reached 3 to 8 mm in diameter. The increase in estradiol concentrations during proestrus, via positive feedback to the hypothalamus, initiates the LH surge, which in turn causes ovulation and the subsequent formation of corpora lutea (CL) and progesterone secretion by the ovary (Fig. 56-1). In the bitch the initial increase in progesterone secretion coincides with the LH surge. Although the onset of behavioral estrus usually occurs within a day or two of the LH surge, behavioral estrus may occur as early as 4 days before or as late as 6 days after the LH surge. Therefore the day on which a bitch allows copulation is not closely associated with the LH surge or ovulation.

In most bitches ovulation occurs within 48 hours of the LH surge (the range is 0 to 96 hours). Ovulation from both ovaries is apparently completed within 24 hours. Primary oocytes (prophase I) are ovulated and resume meiosis during tubal transport. By 2 to 3 days after ovulation, oocytes have matured (metaphase II) and fertilization can occur. Mature oocytes have a fertile life of 2 to 4 days, perhaps longer. The



FIG 56-2
Canine breeding behavior. A, Flagging and standing. B, The postcoital tie.

time during which mature oocytes are available for fertilization has been referred to as the fertile period. Although semen is initially deposited in the cranial vagina during copulation, the large volume of prostatic fluid and the postcoital tie force semen through the cervix (see Fig. 56-2). For that reason dogs are considered among the species having intrauterine semen deposition during natural mating. Fertilization occurs in the uterine tubes. Sperm transport is enhanced by vaginal and uterine contractions that spontaneously occur with natural mating but not during artificial insemination. Freshly ejaculated canine sperm bind to the uterine crypts and glands and to the distal uterine tube, which serves as the sperm reservoir. The sperm reservoir maintains sperm viability between insemination and ovulation, regulates sperm capacitation to synchronize sperm function with ovulation, and controls sperm transport in the uterine tube. Canine sperm remain capable of fertilization in the female tract for 3 to 4 days and occasionally for as long as 6 days. Some sperm can be found in the female tract up to 11 days. The end of the fertile period is thought to be due to oocyte aging, but changes in the cervix and uterine tube environment also play a role.

# **Breeding Management**

Because of the importance of territorial and social dominance to canine reproduction, the usual practice is to take the bitch to the stud for breeding. To optimize conception rates and litter size, viable sperm that are capable of fertilization and mature oocytes that are capable of being fertilized must be present simultaneously. This can be accomplished by a number of different strategies. A common practice is to begin breeding on a predetermined day of the cycle and to breed every other day for as long as behavioral estrus lasts or for at least two breedings. Often, day 10 to day 12 after

the onset of proestrus is chosen. Because the average length of proestrus is 9 days, bitches experiencing an "average" cycle would be in estrus at that time. Because the LH surge usually occurs close to the onset of behavioral estrus, because ovulation usually occurs 2 days after the LH surge, because ova would be fertilizable 2 days later, and because freshly ejaculated semen is capable of fertilization for 4 days, this method of breeding management is usually successful. On the basis of data from artificial insemination programs, two breedings during the fertile period increase conception rates and litter size. Breeding every other day is certainly acceptable but probably unnecessary for animals with normal fertility, provided that at least two breedings are done during the fertile period.

The management scheme of breeding on a predetermined day of the cycle is often modified according to the behavior of the bitch and occasionally according to the behavior of the stud. Bitches not in estrus will not allow copulation. Putting the breeding pair together for supervised periods (15 to 60 minutes) and observing their behavior, a practice called *teasing*, will enable the manager to identify the first day of behavioral estrus; breeding can be done every 2 to 3 days thereafter throughout estrus. Certain males will occasionally show distinctly greater interest in breeding on a particular day during estrus than on other days of that cycle. Some kennel managers believe that such behavior in a male signals the optimal time for insemination, citing excellent conception rates and large litters from these males as validation.

Vaginal cytology is a very useful adjunct to these management schemes, especially in instances in which the female does not exhibit strong behavioral estrus or in which the breeding pair is separated geographically, necessitating transportation of the animals or the semen. The changes in the exfoliated cells reflect the effects of estrogen on the vaginal

epithelium. Under the influence of estrogen, the vaginal epithelium changes in thickness from a thin layer (2 or 3 cells) of stratified squamous cells without cornification to many cell layers in depth with prominent cornification and rete pegging. The epithelial cells exfoliate easily. Vaginal cytology is an excellent bioassay for estrogen that can be used to monitor the follicular phase of the ovarian cycle. As the cytologic changes in proestrus approach those characteristic of estrus, the animal or the semen should be shipped to ensure safe arrival for insemination during the fertile period. Females that do not show normal behavioral estrus during the time that the findings of exfoliative vaginal cytology are consistent with estrus (i.e., greater than 90% superficial cells) could be bred using artificial insemination.

The success of these management methods is predicated on the assumptions that ovulation will occur sometime during behavioral and cytologic estrus and that multiple inseminations will ensure that viable sperm, capable of fertilization, are present whenever ovulation and oocyte maturation actually do occur. When the LH surge is identified and used in conjunction with the other management tools, the certainty that insemination is performed during the optimal fertile period is enhanced. The practice of using the LH surge to determine when to breed has been referred to as ovulation timing. Ovulation timing is especially helpful in situations in which gamete viability is less than optimal, such as with aged bitches or when frozen-thawed semen is used. The LH surge can be identified by measuring serum LH concentrations daily or by identifying the preovulatory increase in the serum concentrations of progesterone that coincides with the LH surge in bitches. Inseminations should be done 4 to 6 days after the LH surge. Interpretation of LH and progesterone results is discussed in greater detail in the section on the assessment of reproductive hormones.

Unlike the situation with queens, breeding a bitch several times during the same day appears to offer no advantage over breeding a single time on a given day. The day of insemination with respect to the occurrence of ovulation is more important than the number of inseminations per day. As the time between insemination and the fertile period lengthens, both conception rates and pups per litter decrease. Conception rates and litter size are also affected by maternal age. Conception rates, litter size, and neonatal survival are greatest for Beagle bitches between 2 and 3.5 years of age. After 5 years of age the conception rate and litter size decline, and neonatal mortality begins to increase. Similarly, in Labrador Retriever, Golden Retriever, and German Shepherd Dog bitches studied from 1 to 10 years of age, it was found that the number of pups born declines when bitches are 7 years of age or older. Litter size differs among breeds, with the bitches of smaller breeds tending to have fewer pups per litter because they produce fewer ova.

# Diestrus

There are no external signs to mark the onset of diestrus other than the cessation of the signs of estrus. The beginning of diestrus is marked by an abrupt change in vaginal cytology. It is characterized by a sudden reduction in the number of superficial cells and the reappearance of intermediate cells, neutrophils, and background debris. Diestrus represents the luteal phase of the cycle. The serum progesterone concentration increases rapidly during the first 2 weeks after ovulation (see Fig. 56-1). It peaks at 15 to 80 ng/ml (approximately 47 to 250 nmol/L) by 15 to 30 days after ovulation. The luteal secretion of progesterone depends on pituitary LH and prolactin. The plasma progesterone concentration remains elevated but gradually declines during the next 2 months regardless of whether pregnancy occurs. In pregnant bitches there is a rapid prepartum drop in the progesterone concentration to less than 2 ng/ml (approximately 6.4 nmol/L). This occurs approximately 64 days after the LH surge and approximately 24 hours before the onset of parturition. The decline in the progesterone concentration may be more gradual in nonpregnant bitches and may not reach basal levels of 0.2 to 0.5 ng/ml (approximately 0.6 to 1.6 nmol/L) for 75 to 90 days. Specific luteotropic or luteolytic factors produced by the canine uterus or placenta that regulate ovarian CL function have yet to be identified. For example, the canine endometrium produces prostaglandin during pregnant and nonpregnant states, but this does not cause earlier CL regression in nonpregnant bitches. Although LH and prolactin are luteotropic in bitches, luteal regression appears to occur after a predetermined life span irrespective of the continuing availability of LH. Parturition and signs of false pregnancy (see Chapter 58) are the only clinical evidence of the end of diestrus. Endocrinologically, diestrus ends when the serum progesterone concentrations decline to less than 1 ng/ml (approximately 3 nmol/L).

# Anestrus

Anestrus follows diestrus and ends with the onset of proestrus of the next cycle. The interval from the end of diestrus, as defined by basal serum progesterone concentrations, to the onset of proestrus is quite variable but averages 4.5 months. Because there are no external signs associated with anestrus, this phase of the cycle has been described erroneously as a period of sexual quiescence. In fact, the pituitary-ovarian axis and the uterus are active during anestrus. Pulsatile secretion of the pituitary hormones LH and FSH continue throughout. During anestrus the endometrium sloughs. The size and activity of the endometrial glands and the thickness of the myometrium and endometrium all decrease, although not to the parameters seen in prepubertal bitches. Endometrial repair continues for about 120 days after nonpregnant cycles and for slightly longer (150 days) after a pregnant cycle. The duration of anestrus per se is rarely determined in clinical practice because anestrus has no external indicators. Rather, the interestrous interval, the onset of proestrus of one cycle to the onset of proestrus of the next cycle, is usually described. The interestrous interval is not lengthened by pregnancy or lactation.

#### THE QUEEN

Female cats are seasonally polyestrous. Cyclicity is controlled by the photoperiod, which must be approximately 12 to 14 hours of light with an intensity of 50 foot-candles. Melatonin appears to be the signal of photoperiod in domestic cats. Cats exposed to natural light usually cease cycling during short days of winter, whereas cats in equatorial photoperiods or maintained under artificial light often cycle throughout the year. It has been shown that maintaining 14:10 to 16:8 hour light: dark schedules maximizes the number of cycling queens in the colony. In the presence of adequate light, sexual maturity and the first estrous cycle normally occur at 6 to 9 months of age, with a range of 5 to 12 months. Unlike bitches, which ovulate spontaneously, queens are induced to ovulate by coital stimulation of the vagina. In addition to coitusinduced ovulation, many domestic cats also have cycles in which spontaneous ovulation occurs.

The follicular phase of the cycle is characterized by increasing serum concentrations of estradiol 17- associated with the onset of proestrus and estrus. Because there is negligible vulvar swelling or discharge in queens compared to bitches, proestrus and estrus are usually recognized by behavioral changes. When it is observed, the vulvar discharge is a clear fluid. Proestrus is characterized by rubbing, treading with the rear feet, vocalization, and decreasing hostility toward the male, although queens will continue to strike at the tom. Proestrus may be so short as to be unrecognized, but more typically it lasts 1 to 2 days.

Estrus is characterized by increased vocalization, rolling, lordosis, holding the tail to one side, and allowing copulation. The characteristic estrual posture can sometimes be elicited by stroking the perineum (Fig. 56-3). Tremors of the body or tail may also be seen. The cytologic appearance of exfoliated vaginal epithelial cells during the estrous cycle is similar to that of bitches, except that red blood cells are much less common. The duration of estrus among queens is quite variable but averages 5 to 8 days. Its duration is not influenced by copulation. Anovulatory cycles occur every 2 to 3 weeks (average 18 days with 12 hours of light) as long as light is adequate. There may or may not be a short *interestrous* period of a few days.

Ovulation occurs as a result of a neuroendocrine reflex that is initiated by the mechanical stimulation of sensory



FIG 56-3
Estrual posture of the queen.

receptors in the vagina and cervix. This sensory input causes a surge of LH to be released from the pituitary gland (Fig. 56-4), which in turn causes ovulation. A high level of estradiol is also required for ovulation. The precise intensity of the copulatory stimulation necessary to induce the LH surge is unknown but varies among queens. The frequency of coital stimulation is apparently the single most important determinant of ovulation in cats. A single copulation induces the LH surge necessary for ovulation in approximately 50% of cats, whereas more than 90% of normal domestic shorthair cats ovulate if bred 3 times daily for the first 3 days of estrus. The day of estrus on which mating occurs and the duration of estrus have no apparent effect on ovulation, except insofar as the concentration of estradiol varies. Once the LH surge occurs, hormonal responses to additional copulatory stimuli are diminished. Ovulation occurs approximately 48 hours after the LH surge. Although cats continue to be referred to as induced ovulators, it is also clear that many cats (35% to 60%) also ovulate spontaneously, in the absence of coital stimulation or direct physical contact with other cats.

After intromission and ejaculation, the queen emits a characteristic scream that signals to the male to dismount. Despite willing acceptance of copulation moments before, queens will attack the tom at this time. Because cats often prefer seclusion, breeding may not be witnessed by the owner. The queen's scream may be the only evidence that mating has occurred. The queen then begins frenzied rolling and grooms her perineum for several minutes and aggressively rebuffs the male. When this "after-reaction" subsides, the queen allows another mating, by either the same tom or another one. Mating frequency is greatest during the first 2 hours (average of five copulations per hour), after which the frequency decreases to about one copulation per hour for the next 3 days. To ensure adequate copulatory stimulation to induce ovulation, three breedings per day for the first 3 days of estrus are recommended. Semen is deposited in the vagina during copulation. The cervix and uterotubal junction are barriers to sperm transport in the cat. The cervix is open on the first day of estrus in both ovulatory and nonovulatory cycles. It is closed when estradiol concentrations fall and when progesterone concentrations rise. As with the bitch, the queen's uterine contractions during mating promote sperm transport. The uterotubal junction and uterine crypts are sperm reservoirs before ovulation, and the tubal isthmus is the reservoir near ovulation.

Because of the territorial nature of cats, especially males, the queen should be brought to the stud. The two should be placed together for short periods so that their behavior can be observed. In this way the manager can be confident that matings have occurred; conversely, the cats can be separated if fighting occurs. This supervised mating scheme may be the best way to optimize conception, but it is labor intensive. Some managers prefer to house the queen and tom together and allow mating to occur ad libitum, without direct observation. In some large breeding colonies, harem, rather than individual, mating schemes are used. In the harem scheme,

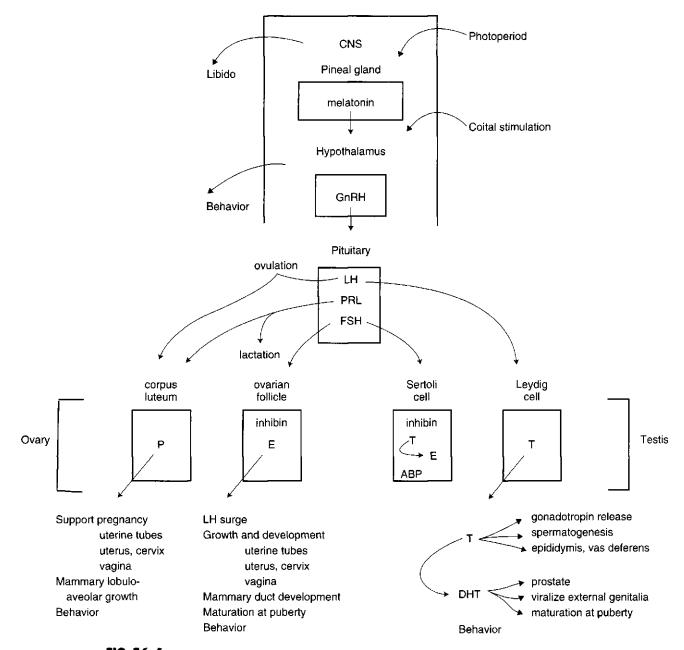


FIG 56-4
Hypothalamic-pituitary-gonadal axis. ABP, Androgen-binding protein; DHT, dihydrotestosterone; E, estrogen; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; P, progesterone; PRL, prolactin; T, testosterone.

one or two toms are housed with several queens. Even though both toms have equal access to the queens, the dominant male usually does most of the breeding. This method is the least labor intensive but has the disadvantages of unknown breeding dates, unknown paternity if more than one tom is involved, and delayed recognition of subfertility in individual animals.

After ovulation the follicles luteinize and produce progesterone. This is the luteal phase of the cycle. Serum concentrations of progesterone rise 24 to 48 hours after ovulation and peak 25 to 30 days later. As with bitches, luteal progesterone is necessary for the maintenance of pregnancy. The corpora

lutea continue to produce progesterone throughout the approximately 65-day gestation (Fig. 56-5), with the serum concentrations gradually declining during the second half of pregnancy. Contrary to what was previously thought, the feline placenta either does not secrete progesterone or does so in amounts insufficient to maintain pregnancy. Serum concentrations of estradiol increase in late pregnancy in cats. Although estrous behavior has been observed in pregnant queens, true superfetation has not been proved.

There apparently are pregnancy-specific luteotropic hormones from the feline placenta or pituitary that control the life span of the corpus luteum. After the nonfertile induction

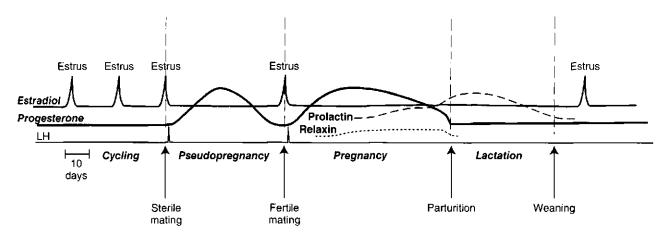


FIG 56-5
The feline estrous cycle.

of ovulation (i.e., when the animal is not pregnant), the corpora lutea persist for about 30 to 40 days. The next cycle may begin any time thereafter, usually within 10 days. In one colony the average interestrous interval was 61 days in queens that were bred but did not conceive, whereas the average interestrous interval for nonbred, anovulatory queens was 22 days. Serum concentrations of progesterone were not determined in those cats.

Litters typically consist of two to five kittens. Queens usually do not resume cycling while they are nursing a litter. Estrous behavior is usually evident 2 to 3 weeks after weaning, although this is quite variable. The postpartum estrus is shorter in duration and less fertile than others. Litter size and neonatal survival are best for queens age 1 to 5 years, provided that first parity occurs before 3 years of age. Litter size and neonatal survival usually improve after the first parity. However, if the first parity occurs after 3 years of age, litter size and neonatal survival usually remain poor. Reproductive performance declines after 6 years of age. Because of decreased fertility, decreased litter size, increased neonatal losses, and the increased prevalence of other illnesses in older queens, most should be retired from breeding after 8 years of age.

# DIAGNOSTIC TESTS FOR THE REPRODUCTIVE TRACT

#### **VAGINAL CYTOLOGY**

The importance of exfoliative vaginal cytology in breeding management and in the evaluation of females with reproductive disorders cannot be overemphasized. Vaginal cytology is used to determine the stage of the estrous cycle, determine breeding and whelping (see Chapter 58) dates, and identify the nature of certain abnormal processes within the reproductive tract (see Chapter 57). Specimens may be obtained with a moistened, cotton-tipped swab or by flushing and aspirating a small volume of saline solution from the vagina. Specimens can be stained with any

number of commercially available stains, including Wright's, Wright-Giemsa, modified Wright-Giemsa (Diff-Quik; Baxter Scientific), trichrome, or new methylene blue. The number and morphologic characteristics of vaginal epithelial cells are evaluated. The preparations are also examined for the presence of other material, such as bacteria, white blood cells, red blood cells, mucus, cellular debris, endometrial cells, or neoplastic cells.

The vaginal epithelium changes dramatically under the influence of estrogen, a process known as cornification. During early proestrus the noncornified parabasal and intermediate vaginal epithelial cells are the predominant cells (more than 80%). As proestrus progresses, the population of exfoliated cells gradually matures; parabasal and intermediate cells disappear as superficial (cornified) cells increase in number. At the end of proestrus superficial and anuclear squamous cells account for 70% to 80% of the epithelial cells. White blood cells decrease in number. Extracellular bacteria may be present throughout proestrus and estrus (Fig. 56-6).

A predominance of superficial cells, an absence of neutrophils, and a clear background characterize vaginal cytologic specimens obtained during estrus. During estrus 90% or more of the epithelial cells are superficial and anuclear squamous cells. White blood cells are normally absent during estrus. Red blood cells and extracellular bacteria are often present (see Fig. 56-6). The beginning of diestrus is marked by an abrupt change in vaginal cytology. Diestrus is characterized by a sudden reduction in the number of superficial cells and the reappearance of intermediate cells, neutrophils, and background debris. On the first day of cytologic diestrus, parabasal and intermediate cells outnumber the superficial and anuclear squamous cells. Sheets of intermediate cells are also often observed. White blood cells return in high numbers during the first day or two of diestrus. Red blood cells and bacteria disappear. The initial dramatic change in cytologic appearance is followed by a gradual change to the anestrual cytologic appearance. On the basis of the examination of only a single cytologic specimen, proestrus cannot

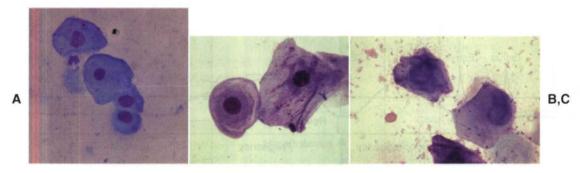


FIG.56-6
Vaginal cytology of estrus. **A**, parabasal and intermediate cells. **B**, Intermediate and superficial cells. **C**, Anuclear squamous cells.

necessarily be distinguished from diestrus. The vaginal cytology of anestrus is quite acellular; it contains primarily parabasal cells and a few small intermediate epithelial cells. The transition from proestrus, through estrus, and into diestrus is usually adequately monitored by cytologic studies done every 2 or 3 days.

#### VAGINOSCOPY

Vaginoscopy is useful for evaluating animals with lower urinary tract signs or urinary incontinence, vulvar discharge, infertility, and anatomic abnormalities; for determining the nature and extent of lesions within the vestibule and vagina; and for identifying the stage of the estrous cycle. Samples for cytologic, microbiologic, and histopathologic studies can easily be obtained through the endoscope. Assuming that the clinician has access to the proper equipment, laser surgery can also be performed. Complications resulting from vaginoscopy, which include hemorrhage, laceration, and introduction of infection, are uncommon with proper technique. Endoscopic findings are assessed by comparing them to the normal anatomic features of the vagina, often in conjunction with vaginal cytology. The endoscopic appearance varies tremendously with the stage of the estrous cycle.

The canine vagina is quite long. In Beagles, for example, it measures 10 to 14 cm in length and 1.5 cm in diameter, whereas in Newfoundlands the length may be up to 29 cm. The endoscopic equipment must be of the appropriate size for the particular female. Proctoscopes and cystoscopes designed for human pediatric or adult patients or flexible fiberoptic endoscopic equipment of appropriate diameter can be used. Pediatric anoscopes or veterinary otoscopes may be narrow enough for use in queens and small bitches but are too short for examination of the cranial vagina and cervix.

In bitches that are in heat, vaginoscopy is usually performed with the animal awake and standing and without sedation or anesthesia unless a biopsy is planned. Anesthesia is necessary for vaginoscopy in queens, small bitches, and puppies and when cystoscopes with saline infusion to distend the vagina will be used. The perineum is inspected and cleansed. The endoscope is then lubricated with warm saline solution or with sterile, water-soluble lubricant. The clitoris



FIG 56-7 Vaginoscopy demonstrating the vestibulovaginal junction in a 1-year-old, spayed female retriever with lympho-nodular urethritis causing persistent pollakiuria.

and clitoral fossa must be avoided. Therefore the endoscope is passed in a dorsal direction through the dorsal commissure of the vulva. There will be increased resistance at the narrow vestibulovaginal junction (Fig. 56-7) in all but estrual bitches. It is especially narrow in prepubertal and neutered animals. The angle of the speculum is adjusted to be more parallel with the spine after it passes through the vestibulovaginal junction.

During proestrus the longitudinal folds of the vagina are edematous, round, and smooth. As new folds develop, the vaginal lumen becomes filled with folds. A clear, bright-red fluid is seen in the vaginal lumen, sometimes in large amounts. As estrus approaches, the vaginal folds become lower and wrinkled. During estrus the folds appear sharp, angular, and crinkled. The mucosa is pale, and the vaginal lumen is wide. There is less luminal fluid than there is during proestrus. This fluid is clear and usually straw colored; however, it may continue to be bright red throughout estrus.

During diestrus (the luteal phase) the vaginal folds are low, round, and soft. The folds in the cranial vagina have a characteristic rosette appearance and may be mistaken for the cervix. Clear or opalescent mucus is present in the vaginal lumen during diestrus. The vaginal mucosa has streaks of hyperemia. During anestrus and in neutered bitches, the vaginal folds are low and round and do not fill the lumen. There is a thin mucous coating that gives the mucosa a translucent, pink-red appearance. In these animals the mucous membranes are thin and easily traumatized. Pinpoint submucosal hemorrhages may develop in response to seemingly gentle contact with the endoscope. During anestrus and in neutered animals there is usually some resistance to the passage of the endoscope unless the instrument is very well lubricated.

In bitches one of the vaginal folds, known as the *dorsal median postcervical fold*, is often mistaken for the cervix. This fold extends from the caudal-dorsal edge of the vaginal portion of the cervix along the dorsal midline and eventually blends into lesser folds of the vagina. It is composed of longitudinal and oblique smooth muscle bundles and irregularly arranged collagen. Unlike other folds of the vagina, the dorsal median fold has no elastic fibers. In Beagle-size bitches, this fold is 15 to 42 mm long and 2 to 10 mm wide, compared with the average vaginal length in the same bitches of 158 ± 30 mm. The lumen of the cranial vagina in this area is quite narrow. Because of its length, location, and inelastic nature, the dorsal median postcervical fold often prevents visualization and catheterization of the canine cervix.

The vaginal portion of the cervix is tubular, with small furrows radiating from the os, which give it the appearance of a star or rosette. The cervical os is not obviously "open," even if fluid is seen flowing through it, except during the puerperium. The vaginal lumen around the cervix and the cranial aspect of the dorsal median postcervical fold is quite narrow, and except during estrus the use of small-diameter (0.5 cm) instruments is usually necessary to visualize the cervix. The narrow pericervical vaginal lumen with the dorsal median postcervical fold and the rosette appearance of the cranial vagina can be confused with the cervix.

#### VAGINAL BACTERIAL CULTURES

Bacterial infections of the reproductive tract are relatively common. Bacterial culture is indicated for the evaluation of many reproductive disorders, including infertility, vulvar discharge, pyometra, metritis, abortion, and stillbirth. Because the uterus is usually sterile, except in some bitches during proestrus and estrus, the interpretation of uterine culture results is relatively straightforward. Unfortunately, because of the difficulty in catheterizing the cervix in the bitch or queen, uterine samples are usually obtained only during laparotomy. Vaginal cultures are usually performed in lieu of uterine cultures. To minimize contamination from the vestibule and caudal vagina, samples for bacterial culture should be obtained from the cranial vagina using a guarded culture swab (e.g., those manufactured by Kalayjian Industries and Nasco) or through a sterile speculum.



BOX 56-1

#### Normal Bacterial Florae of the Canine Vagina

#### Aerobic Bacteria

Pasteurella multocida

β-hemolytic Streptococci

Escherichia coli

Unclassified gram + rods

Unclassified gram - rods

Mycoplasma

α- and nonhemolytic Streptococci

**Proteus** 

Bacillus

Corynebacterium

Coagulase-positive and coagulase-negative Staphylococci

**Pseudomonas** 

Klebsiella

Neisseria

Micrococcus

Haemophilus

Moraxella

Acinetobacter Flavobacterium

Lactobacillus

Enterobacter

. . . . . .

#### Anaerobic Bacteria

Bacteroides melaninogenicus

Corynebacterium

Haemophilus aphrophilus

Bacteroides

Enterococcus

Peptostreptococcus (hemolytic and nonhemolytic)

Ureaplasma

The canine vagina has normal bacterial florae, which are listed in Box 56-1. Only 2% of 826 specimens obtained from intact bitches were negative for bacterial growth (Bjurström et al., 1992), whereas 23% of 66 specimens from queens were negative (Ström-Holst et al., 2003). In order of reported frequency, the most commonly isolated organisms from bitches are Pasteurella, Streptococci, and Escherichia coli. With the exception of Mycoplasma, anaerobic organisms are much less commonly isolated than aerobic. Cultures from bitches usually yield mixed populations of bacteria; however, in Bjurström's study 18% were a growth of only one organism. The florae vary within and among individuals and throughout the cycle. The normal florae of the feline vagina are similarly diverse. E. coli, Staphylococcus, and Streptococus canis are the most common organisms recovered from queens. Unlike the situation in bitches, a single organism (most often E. coli) is isolated from 41% of cats. Anaerobic organisms are uncommon in queens. Even in normal bitches and queens, organisms may be recovered in large numbers.

Most of the organisms that make up the normal vaginal florae are also potential pathogens. Several studies have shown that there are no differences among the bacterial isolates from normal fertile bitches, infertile bitches, and bitches with evidence of genital disease. Isolation of opportunistic pathogens from the vagina is therefore not proof of infection. Thus the results of vaginal cultures and the potential role of the isolated organisms in the pathogenesis of the clinical signs must be interpreted cautiously. *Brucella canis* (see Chapter 58) is always considered a pathogen, even in the absence of clinical signs. The role of *Mycoplasma* spp. and *Ureaplusma* spp. in reproductive disorders in cats and dogs remains unclear.

## **VIROLOGY**

Viral diseases may cause reproductive problems by directly affecting reproductive organs or because of the systemic illness they cause in the pregnant female. Respiratory disease and neonatal death are the most common manifestations of canine and feline herpes infection. Canine herpes virus also causes apparent failure to conceive; abortion; and, less commonly, genital lesions. Rarely, vesicular lesions may be found on the mucosa of the vestibule or prepuce of infected dogs. The most important route of transmission is oronasal contact with infected secretions. Transplacental and venereal transmission are much less important. The virus may be isolated from nasal, conjunctival, tracheal, vaginal, or preputial scrapings for 2 to 3 weeks after acute infection. Thereafter virus isolation and polymerase chain reaction (PCR) are usually negative. Because canine herpesvirus is poorly immunogenic, virus-neutralizing antibodies are present in small amounts for short periods. The finding of any detectable titer in the presence of compatible clinical signs is therefore considered significant. Fetal and neonatal necropsy findings are generalized, multifocal hemorrhages in kidney, lung, and liver and necrotic foci with intranuclear inclusion bodies. In queens panleukopenia, calici virus, feline infectious peritonitis, and feline leukemia virus infection are reported to be potential causes of infertility, abortion, and neonatal death.

# ASSESSMENT OF REPRODUCTIVE HORMONES

Measurement of serum concentrations of reproductive hormones can be useful in evaluating animals with suspected or known reproductive disorders. The reproductive hormones are released in cyclic, episodic, or pulsatile manners; therefore the results of a single determination often are not diagnostic because the phase of the cyclic release at the time of sample collection is unknown. For that reason, repetitive determinations performed over the course of hours, days, or weeks, or provocative testing, may be necessary. Most hormone assays, such as radioimmunoassays (RIA), chemiluminescent, and enzyme-linked immunosorbent assays (ELISA), depend on immunologic reactions. Errors can result if antibodies or antigens in homologous assay systems are not species specific and if species-specific interference with antibody binding occurs in heterologous systems. For these reasons, it is critical that each laboratory validate its procedures and determine reference ranges for each species and each hormone to be tested.

# **Progesterone**

As the time of ovulation approaches during estrus, ovarian follicular cells transform from estrogen-producing to progesterone-producing cells. LH causes ovulation and thus is responsible for this transformation. After ovulation, the follicles become CLs and produce progesterone. The stage of the ovarian cycle during which progesterone concentrations are high is called diestrus. If conception occurred, the length of diestrus will be the length of gestation. Gestation averages 65 days after breeding in the queen and 63 days after breeding in the bitch. If conception did not occur in a queen that did ovulate, the CLs will regress in 30 to 40 days. The bitch, on the other hand, is unique among common domestic animals in that the CLs persist and produce progesterone for 60 or more days, irrespective of pregnancy status. The CLs are the only significant source of progesterone in the pregnant bitch and queen and are required to maintain pregnancy throughout. Progesterone concentration must drop to basal levels for parturition to occur. It remains at basal levels through anestrus, until ovulation during the next estrous cycle (see Fig. 56-1).

In the bitch progesterone concentrations begin to increase above basal levels as a preovulatory event. This initial rise occurs simultaneously with the LH surge. Therefore progesterone can be used to approximate the LH surge and predict impending ovulation in the bitch. In the queen the initial rise above basal progesterone concentration occurs after the LH surge. In both the bitch and queen, high progesterone concentrations are indicative that ovulation did occur. The next cycle will not begin until sometime after progesterone has returned to basal levels.

There are a wide variety of laboratory methods used to detect progesterone. These include RIA, which is considered to be the gold standard, and chemiluminescent immunoassay (CLIA). These are available from several commercial laboratories with "same-day" results. Lower values are obtained using CLIA than RIA. Results may be reported in ng/ml or nmol/L. The conversion from one unit to the other is (ng/ ml)(3.18) = (nmol/L) of progesterone. It is essential to use the reference ranges established by the laboratory for its methodology and validated for use in the particular species. The advantage of RIA and CLIA is quantitative results. There are point-of-care tests based on ELISA and rapid immunomigration (RIM) method (Ovucheck® Premate, Synbiotics Corp.). These provide semiquantitative results in three ranges. The low range is usually less than 3 ng/ml (less than approximately 9.5 nmol/L), the midrange is from approximately 3 ng/ml to 10 ng/ml, and the high range is greater than approximately 10 ng/ml (approximately 31.8 nmol/L), depending on the kit manufacturer. The midrange of the kit is designed to correlate with the LH surge in the bitch and is used to predict that ovulation will occur in 3 to 6 days. Compared with RIA or CLIA, the semiquantitative, in-house kits have been found to be 80% to 90% accurate in determining progesterone concentrations in dogs and cats. Nevertheless, some practitioners find them useful. Storage time, temperature, contact with red blood cells, contact with serum

separator gel, and anticoagulants affect the results. Therefore the laboratory or kit manufacturer's recommendations for sample handling must be followed. Samples for progesterone determination must never be drawn into serum separator tubes because the results will be spuriously decreased.

One of the most common reasons to measure progesterone in bitches is to determine the optimal time to breed. It is used in two ways. One is to approximate the time of the LH surge, a practice known as ovulation timing. It is based on the fact that in bitches the serum progesterone concentration increases to more than 1 to 2 ng/ml (approximately 3 to 6 nmol/L) at or shortly before the preovulatory LH surge. Therefore serial determinations (every 2 to 3 days) of the serum progesterone concentration during proestrus, to identify the initial increase above 2 ng/ml, can be used to estimate the time of ovulation, which follows the LH surge by about 2 days. As discussed earlier, fertilization could occur about 2 days after ovulation. Therefore the recommendation is to breed 3 to 6 days after the initial rise in progesterone (i.e., the LH surge) is detected. The other way progesterone concentrations are used to determine breeding day is based on the knowledge that fertilization could occur about 2 days after ovulation, during which time progesterone concentration has been rapidly increasing. Serum concentrations of progesterone greater than 8 ng/ml (25.4 nmol/L) are interpreted to indicate that ovulation has occurred. Analysis of several independent breeding trials in which serum concentrations of progesterone were determined on the days of insemination revealed that pregnancy rates were best when insemination was performed on days that serum progesterone concentrations were greater than 8 ng/ml (greater than 25.4 nmol/l) and up to 19 to 26 ng/ml (approximately 60 to 80 nmol/L). Two inseminations, 48 hours apart, are recommended, unless the initial progesterone is already near 19 ng/ ml (60 nmol/L), in which case the second insemination is done the next day.

Finding the increased serum concentrations of progesterone indicative of ovulation would be of interest in females suspected of having ovulation failure. In the case of queens this may be due to inadequate copulatory stimulation to induce the LH surge. Finding high progesterone would also confirm ovulation in an animal suspected of having had a "silent" or unobserved heat, or it could confirm the presence of an ovary in an animal suspected of having an ovarian remnant after being spayed. The adequacy of luteal function during pregnancy can be monitored by determining serum progesterone concentrations once weekly for about 9 weeks after breeding or until parturition. This would be of interest in females in which inadequate luteal function (premature luteolysis; hypoluteoidism) was the suspected cause of unexplained abortion. It would also be useful in monitoring the effectiveness of certain abortifacient drugs. In pregnant bitches (but not necessarily in pregnant queens), parturition normally occurs within 24 hours after serum progesterone concentration decreases below 1 to 2 ng/ml (approximately 3 to 6 nmol/L). Therefore impending parturition can be predicted by monitoring the serum progesterone concentration.



BOX 56-2

### Indications for Measuring Serum Progesterone

#### Ovulation timing

- Identify LH surge, breed 3 to 6 days later
- Identify fertile period, progesterone approximately 10 to 26 ng/ml

#### Infertility

- Confirm that ovulation did (high progesterone) or did not (low progesterone) occur
- High progesterone would be found in cases of luteal cyst
- Confirm that induction of ovulation was successful Assess corpus luteum function
- Monitor the effectiveness of certain abortifacient agents
- In cases of spontaneous abortion, assess for premature luteolysis or hypoluteoidism
- · Identify that a "silent" heat occurred
- Identify ovarian remnant, high progesterone 5 to 7 days after signs of heat

#### Predict whelping

- Within 24 hours of progesterone less than 2 ng/ml
- 65 ± 1 day from the LH surge

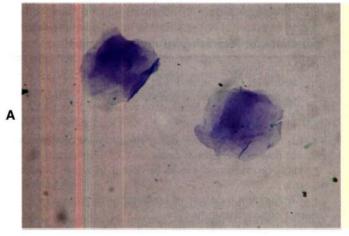
Recognize progesterone-producing testicular tumor

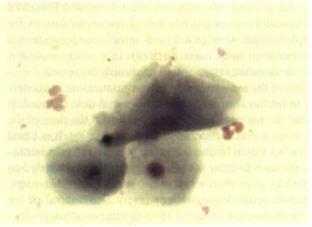
This information would be of use in the management of dystocia and in the planning of cesarean sections (Box 56-2).

#### **Estradiol**

Estradiol-17 $\beta$  is the main estrogen in circulation. The primary source of estradiol in sexually intact females is the ovarian follicle. In both males and females estradiol is also derived in peripheral tissue by the aromatization of testosterone and androstenedione. In sexually intact males the testis produces small amounts of estradiol, but this accounts for only about 20% of estradiol production in dogs. The majority is derived from aromatization of circulating androgens, testosterone and androstenedione. Androstenedione is of adrenal origin. Typical mean serum estradiol concentrations in the bitch are 5 to 10 pg/ml during anestrus, 10 to 20 pg/ml during early proestrus, and 50 to 100 pg/ml during late proestrus. Estradiol concentrations decline through estrus (see Fig. 56-1). During estrus in queens, estradiol is also typically >25 pg/ml to above 50 pg/ml. It returns to basal levels of <15 pg/ml in between cycles and during the seasonal anestrus.

Unfortunately, estradiol concentrations are often at or below the limits of detection of the assays used by many commercial endocrine laboratories. Estradiol concentrations also fluctuate widely and rapidly, and the high concentrations that occur during proestrus may be detectable for only a day or two. Deficiencies in circulating concentrations of estradiol are rarely documented in dogs and cats. Pathologic increases in estradiol production, such as those that occur in animals with ovarian follicular cysts or Sertoli cell tumors,





**FIG 56-8 A,** Vaginal cytology from an 18-month old cat with an ovarian remnant after being spayed 1 year ago. Estrus cycles began a month ago. **B,** Preputial cytology from a 10-year-old, male retriever with an estrogen-producing interstitial cell tumor.

may still be less than the detectable limits of many assays. For these reasons the measurement of estradiol concentrations often does not yield diagnostic results. A simple, accurate means of gauging estrogenic activity in the female is to evaluate vaginal epithelial cells for signs of cornification (see Fig. 56-6). All things considered, vaginal cytology is often preferable to determination of serum concentrations of estradiol in females. The preputial epithelium is also responsive to estrogen, exhibiting changes similar to those of the vaginal epithelium (Fig. 56-8). The paraneoplastic syndromes associated with excessive estrogen in dogs include alopecia, gynecomastia, pendulous prepuce, and bone marrow suppression. In bitches and queens cystic follicles in intact or remnant ovaries may continuously produce estradiol and cause persistent signs of heat and, much less commonly, alopecia. Assessing estradiol or its influence on vaginal epithelium is indicated for determining the stage of the estrus cycle for breeding management and for evaluating females suspected of having an ovarian remnant after being spayed. Finding cornification of vaginal epithelium or very high estradiol concentrations in a supposedly spayed queen or bitch that is displaying characteristic physical or behavioral signs of heat would be consistent with a diagnosis of ovarian remnant. Finding very high estradiol concentrations or the influence of estradiol on vaginal or preputial epithelium in an animal displaying estrogen-induced paraneoplastic syndromes justifies a search for a gonadal source (estrogen-producing testicular tumor, cystic ovarian follicles) or an exogenous source of estrogen. These would be far more likely than an adrenal source of estrogen in species other than the ferret.

# Gonadotropins: Follicle-Stimulating Hormone and Luteinizing Hormone

The gonadotropins, FSH and LH, are produced by the pituitary, under the control of hypothalamic gonadotropin-releasing hormone (GnRH; see Fig. 56-4). As discussed

earlier in the chapter, they are secreted in a pulsatile manner, in ever-increasing magnitude until a so-called surge occurs. The increasing concentrations of FSH at the end of anestrus initiate ovarian follicular development and the onset of the next estrus cycle. The surge of LH causes maturation and ovulation of ovarian follicles, which luteinize and produce progesterone. The duration of the LH surge is relatively short, usually occurring within a 24-hour window, although it may remain elevated for somewhat longer. Additionally, in queens a neuroendocrine reflex initiated by coital stimulation of the vagina also causes the LH surge. In males FSH supports Sertoli cell function and spermatogenesis. LH stimulates testosterone secretion by the Leydig cells of the testis. The gonadal hormones, in turn, feed back to the hypothalamus and pituitary. Following gonadectomy this negative feedback control of LH is lost, and serum concentrations of LH and FSH are persistently elevated. This could also occur with the rare condition of gonadal dysgenesis. The secretory capacity of the pituitary gonadotropins can be assessed by determining LH and/or FSH before and after administration of GnRH. A point-of-care, semiquantitative immunochromogenic assay for LH has been intermittently available (ICG Status-LH®, Synbiotics). Few commercial laboratories offer quantitative assays for LH or FSH for veterinary patients at this time.

As discussed earlier, identification of the preovulatory LH surge is a useful tool in canine breeding management; however, the LH surge lasts only 24 to 72 hours. Therefore frequent sampling (i.e., at least once q24h) is essential to ensure that it is not missed. Because pulses of LH other than the surge may be of sufficient magnitude to be detected by the assay, some clinicians recommend measuring serum concentrations of progesterone several days after the surge. Progesterone concentrations above 2 ng/ml (6 nmol/L) differentiate the actual pre-ovulatory LH surge from the normal proestrus pulses of LH. Trying to determine optimal breed-

ing time with such precision is most applicable when frozen semen is to be used because the life span of thawed spermatozoa is short, perhaps only 24 hours. Because the frequent blood sampling necessary to identify the LH surge is inconvenient and expensive, progesterone concentrations are often assessed in lieu of LH itself to estimate the surge.

To avoid unnecessary laparotomy, serum concentrations of LH can be measured to determine the presence or absence of gonads in animals with unknown reproductive status, such as those newly acquired by shelters or private owners. High concentrations of LH are consistently found from 5 days to as long as 5 years after ovariectomy in bitches. This is because negative feedback from the gonadal hormones to the pituitary is lost. Conversely, LH is also helpful for evaluating females suspected of having ovarian remnants after being spayed. In this situation feedback loops are still intact and LH concentrations will be low except during heat. Finding high serum LH concentrations is sensitive for detecting animals that have been spayed (sensitivity: 100% in 50 queens; 98% in 300 bitches). However, it is not as specific, especially in bitches, because high LH is also normally found in cycling females (specificity: 92% in queens; 78% in bitches). The proportion of animals with high LH that are spayed—in other words, the probability that high LH correctly predicts a spayed animal—is fairly high (positive predictive value: 92% in queens; 90% in bitches) but not perfect, again because intact females also have high LH at some times during the estrus cycle. Therefore females with high LH are either spayed or in heat, which can easily be differentiated by physical examination, vaginal cytology, or measurement of serum progesterone. Males with high LH have been castrated. The proportion of animals with low LH that are actually spaved is very low (negative predictive value: 100% in queens; 96% in bitches). In other words, the probability that finding low LH will correctly predict an intact animal is very high. Females with low LH have not been spayed or have ovarian remnants and are not presently in heat. Males with low LH have one or both testicles. If they are not in the scrotum, the male is cryptorchid. A much less likely cause of low LH in males and females would be exposure to exogenous sex hormones.

FSH is rarely measured in small animal practice, primarily because appropriate assays are usually not commercially available. However, it has been shown that FSH is a more specific indicator of neuter status than is LH in bitches because FSH concentrations are consistently higher in spayed bitches than intact bitches, even during heat.

# **Gonadotropin-Releasing Hormone**

GnRH, which is secreted by the hypothalamus, controls pituitary secretion of FSH and LH in both male and female animals. GnRH assays are not readily available, and GnRH is rarely measured in the small animal practice. However, exogenous GnRH administration can be used to evaluate the pituitary-gonadal axis. After the administration of GnRH to normal dogs and cats, there is a prompt (within 30 minutes) increase in the serum concentrations of LH. The magnitude

of the response is influenced by the stage of the reproductive cycle and the dose of the drug. After the serum concentration of gonadotropins increases in response to GnRH, serum concentrations of gonadal hormones also increase. The degree of gonadal responsiveness understandably varies with the stage of the reproductive cycle in females and whether the male has one, two, or no testes. Failure of serum LH concentrations to increase after GnRH administration points to the possibility of a pituitary problem. Failure of gonadal sex hormones to increase appropriately after GnRH administration indicates either pituitary dysfunction (no increase in LH), gonadal dysfunction, or prior gonadectomy. Administration of GnRH can also be used to induce estrus in the bitch and queen.

# Relaxin

Relaxin is produced primarily by the placenta; therefore it is pregnancy specific in bitches and queens. In pregnant bitches and queens, relaxin reaches detectable levels in serum or plasma as early as 20 days after the LH surge and peaks 30 to 35 days after the LH surge. It remains high throughout pregnancy, until parturition or abortion, when it declines precipitously. Low levels may be detectable for 4 days postpartum in bitches. Although the manufacturer suggests that the test can be useful 21 days after breeding, it is a more sensitive indicator of pregnancy when performed 30 or more days after breeding. There may be an influence of litter size on relaxin concentrations. Finding high concentrations of relaxin in serum or plasma confirms pregnancy. Declining or undetectable concentrations are found in cases of spontaneous or induced abortion and after parturition. Relaxin is undetectable in pseudopregnant and nonpregnant bitches and queens. There are two commercially available point-ofcare assays for relaxin. Witness Relaxin®, a rapid immunomigration assay, can be used for dogs and cats. ReproCHEK® is an ELISA system for use in dogs. (Both assays are from Synbiotics Corp.)

### DIAGNOSTIC IMAGING

Radiology and ultrasonography are useful for evaluating the ovaries, uterine wall, and intrauterine contents; confirming pregnancy; and assessing fetal viability. The normal uterus and ovaries in a nonpregnant animal are not detected by routine abdominal radiography (see Fig. 56-9). During normal anestrus they may be difficult to identify by ultrasonography. Increased size and density and an abnormal shape of the uterus may be detected by either technique. Ultrasonography can be used to evaluate the uterine wall and the intrauterine contents. Ultrasonography may also help identify ovarian remnants, ovarian cysts in animals with persistent estrus and hyperestrogenism (follicular cysts), or persistent anestrus (nonfunctional or luteal cysts). It may be able to identify ovarian neoplasia as well. In males diagnostic imaging is very helpful in evaluating the prostate and testes (see Chapters 61 and 62). Negative findings with diagnostic imaging do not necessarily exclude disease in the reproductive tract, especially in females.

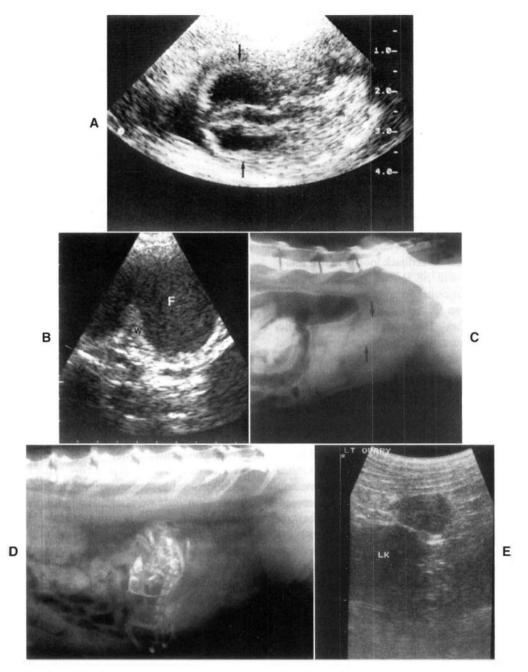


FIG 56-9

**A,** Sonogram of canine gestational sac (arrows) at 29 days. Scale is in centimeters. **B,** Sonogram of canine pyometra showing thickened uterine wall (W) and lumen distended with fluid (F). **C,** Radiograph of feline pyometra showing fluid-filled uterus (arrows). **D,** Radiograph of mummified fetus. **E,** Sonogram of 1.8 × 1.2-cm ovary with corpora lutea in a normal 3-year-old Weimaraner 30 days after estrus. The serum progesterone concentration was 64 nmol/L. LK, Left kidney. (**A** Courtesy Dr. Tom Bell, East Lansing, Mich.)

Because of the difficulty involved in catheterizing the cervix, contrast studies of the uterus and uterine tubes (i.e., hysterosalpingography) are rarely done in bitches and queens. During estrus contrast material deposited in the cranial vagina may enter the uterus and provide a hysterogram, but at other stages of the cycle the cervix is normally closed. Positive-contrast vaginography, using a Foley catheter and a water-soluble contrast agent (e.g., diatrizoates such as

Renografin®), is easily performed, but general anesthesia is necessary. Vaginography can be considered if vaginoscopy fails to clearly identify strictures, anatomic defects, masses, or foreign material in the vagina.

# **KARYOTYPING**

Some intersex conditions and developmental abnormalities of the reproductive tract may be associated with chromo-

somal anomalies (e.g., XXX, XO). These animals are usually seen because of abnormal external genitalia, infertility, or persistent anestrus. Karyotype analysis can be performed if a congenital rather than an acquired cause is suspected and if routine diagnostic tests have failed to identify the cause of the reproductive dysfunction. Cells from any tissue can theoretically be used for chromosomal analysis, but lymphocytes from heparinized blood samples are the usual specimen. (e.g., University of Minnesota Veterinary Cytogenetics Laboratory, Department of Veterinary Pathobiology).

# LAPAROSCOPY AND CELIOTOMY

Exploratory celiotomy is often the most cost-effective way to diagnose and treat intersex animals. In all other circumstances, however, diagnostic laparoscopy or exploratory celiotomy should not be done until a noninvasive diagnostic evaluation of the bitch or queen with a reproductive disorder has been completed. Laparoscopy and celiotomy allow gross visualization of the reproductive tract, bacterial culture of the uterine lumen, and full-thickness biopsy of the uterus. The patency of the uterine horn and uterine tubes might be determined by infusion of sterile saline solution, using the techniques developed for in vitro fertilization and embryo transfer. Laparoscopy and celiotomy are best performed during anestrus to fully appreciate persistent pathologic changes in the uterus.

# FEMALE INFERTILITY

An accurate history is critical to the evaluation of a female animal suspected to be infertile. When taking the history, the clinician should investigate the details of previous cycles, including the dates of onset of each cycle, the female's behavior during estrus, the dates and methods of previous inseminations, the fertility of the studs used, and the events following breeding (Box 56-3). A complete physical examination should be performed to identify (1) potential causes of infertility outside the reproductive tract, (2) other abnormalities that might adversely affect the health of the female or the pregnancy itself should conception occur, and (3) congenital and heritable defects that should exclude this female from a breeding program.

The reproductive tract is then examined. Mammary glands are carefully palpated to assess their size and consistency and the character of any secretions. The vulva is inspected to determine if there are structural abnormalities or any discharge. The labia are separated so that the vestibular mucosa and clitoris (in bitches) can be visualized. The uterus is palpated transabdominally. A vulvar discharge may be more apparent after abdominal palpation. The vestibule and posterior vagina should be palpated with a gloved finger in bitches of adequate size. Rectal palpation may help determine the extent of abnormal structures within the vestibule and caudal vagina.

The history and physical examination findings determine the nature of any additional diagnostic tests to be performed.



BOX 56-3

# Historical Information for Female Infertility

1. What is the present stage of the estrous cycle?

2. Description of previous cycles

Age at puberty

Dates of onset of previous cycles

Lengths of previous cycles

Behavior during proestrus and estrus

Attractive to males?

Allow mounting?

Did intromission occur?

Did insemination occur?

Dates of insemination: How were these dates chosen?

Predetermined day of season

Behavioral changes

Vaginal cytologic findings

Ovulation timing

Method of insemination

Natural

Artificial with fresh, chilled, or frozen semen

3. Assess male fertility

Outcome of breeding to different males, if any

Has this male ever sired a litter? When?

Healthy litters from other females bred by him near the time of breeding the female in question?

Results of recent semen evaluation

4. Events after breeding or after unbred cycles

Early pregnancy diagnosis?

When?

What method?

Physical/behavioral changes?

Palpation?

Ultrasound?

Mammary development, overt false pregnancy?

Vulvar discharge?

Abortion?

**Parturition** 

Length of gestation

Dystocia?

Litter size

Health and survival of puppies or kittens

5. Previous diagnosis and treatment of reproductive problem

Tests performed and their results

Brucella canis

Thyroid profile

Feline leukemia virus

Medications administered

Correlate with stage of estrous cycle

Nonreproductive problems, diagnostic tests, and/or medication

In this individual animal (e.g., glucocorticoids)

In the kennel or cattery (e.g., feline viral rhinotracheitis infection)

Historic or physical abnormalities outside the reproductive tract should be investigated. All dogs should be tested for *Brucella canis* (see Chapter 58) before breeding and before infertility is evaluated further. A complete blood count (CBC), serum biochemistry panel, and urinalysis provide excellent information regarding the overall metabolic health of the animal and could reasonably be included as a routine part of the evaluation of infertility. Only normal, healthy animals in excellent body condition should be bred.

The reproductive history often dictates the nature of the diagnostic approach. Perhaps most important are characterizing proestrus-estrus and the interestrous interval of the female, identifying the criteria used to determine when the female is bred, and determining the female's behavior during mating (see Fig. 56-10). Typically, one of the following four descriptions applies: failure to cycle, abnormal interestrous interval, abnormal proestrus-estrus, or normal cycles.

# **FAILURE TO CYCLE**

There are two subcategories of animals with persistent anestrus. *Primary anestrus* refers to females 24 months of age or older that have never cycled. *Secondary anestrus* applies to females that have previously cycled but are no longer doing so. An animal that has never cycled may be a normal prepubertal animal younger than 24 months of age, may be experiencing "silent" heats, may have a congenital gonadal or chromosomal anomaly, or may have a concurrent disorder that is preventing estrous cycles. Exposure to light may be inadequate to initiate and maintain cyclicity in queens with persistent anestrus. Gonadal dysfunction, concurrent metabolic disorders or medications, and advancing age should be considered in females with secondary anestrus.

Diagnostic tests for persistent anestrus are usually delayed until a female is 2 years of age because of the probability that she is a normal prepubertal animal. Some veterinarians believe that an initial undetected or "silent" first heat cycle is common in bitches. If so, this could explain why some young bitches appear to have persistent anestrus. Unobserved or silent heats may be detected retrospectively by measuring the serum progesterone concentration. If the concentration is greater than basal anestrus levels (>2 ng/ml, or >6.4 nmol/L) in a bitch, a cycle has occurred within the previous 60 to 90 days. The finding of high serum concentrations of progesterone in a supposedly anestrous queen indicates that unobserved estrus has occurred and also that either unobserved mating or spontaneous ovulation occurred within the past 30 to 40 days. Clinical signs of false pregnancy (see Chapter 58) would also indicate that an undetected cycle occurred approximately 60 days earlier. Silent cycles could be detected prospectively by examining vaginal cytology every 1 to 2 weeks. Noncycling females should be housed with cycling females whenever possible because the pheromones from cycling females may induce noncycling females to cycle. Queens should be exposed to at least 12 hours of light for at least 2 months before further testing is done.

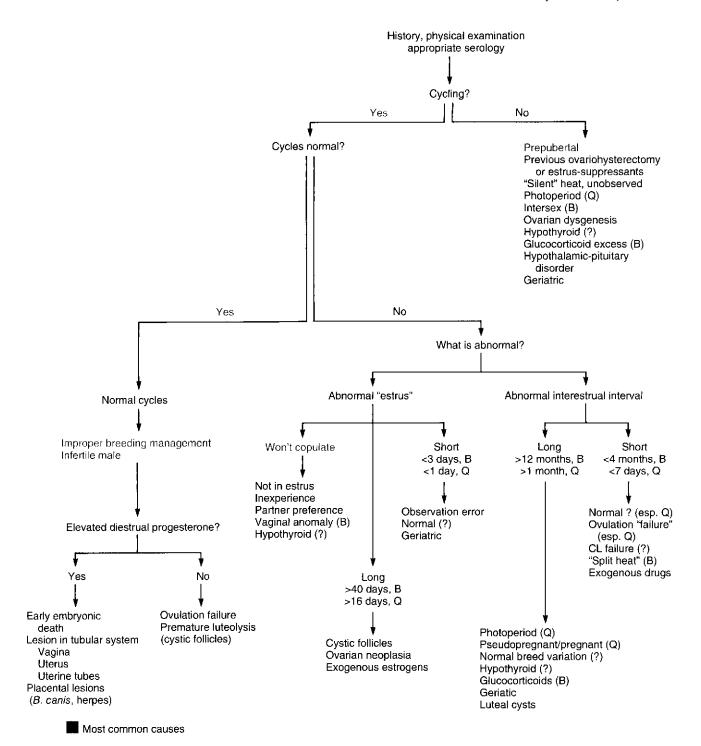
Persistent anestrus may result from suppression of function of the hypothalamic-pituitary-ovarian axis. Hypothyroidism, exogenous glucocorticoid therapy, and concurrent metabolic disease are commonly reported but rarely confirmed causes in bitches. Thyroid function is assessed by measuring serum concentrations of the thyroid hormones and canine thyroid-stimulating hormone (cTSH; see Chapter 51). The role of hypothyroidism in infertility in the bitch has not yet been thoroughly evaluated. Exogenous glucocorticoids are commonly administered to animals and cause many alterations in reproductive function, including prolonged anestrus and abortion. The history should be reviewed to determine if the animal could have received glucocorticoid treatment. In mature bitches increased serum alkaline phosphatase activity in conjunction with relatively normal alanine aminotransferase activity is suggestive of supraphysiologic amounts of glucocorticoids. If there is still doubt about excess endogenous or exogenous glucocorticoids, adrenocortical function can be assessed with an adrenocorticotropic hormone (ACTH) stimulation test. The presence of other concurrent metabolic disease is determined with a CBC, serum biochemistry panel, and urinalysis.

Persistent anestrus may also result from a primary abnormality anywhere within the hypothalamic-pituitary-gonadal axis, including intersex conditions, ovarian dysgenesis, progesterone-secreting luteal cysts, or ovarian tumor. It may also result from previous ovariohysterectomy. Females with ovarian dysgenesis or that have undergone oophorectomy are expected to have chronically increased serum concentrations of LH, which can be measured. Serum progesterone concentrations can be determined to assess functional luteal cysts. The functional status of the hypothalamic-pituitaryovarian axis can be evaluated by measuring serum LH and progesterone concentrations before and after GnRH administration. Ultrasonographic evaluation of the ovaries may identify ovarian abnormalities such as cysts or neoplasia. On close inspection, many apparently female intersex animals have detectable anatomic abnormalities of the clitoris, vestibule, and/or vagina that result from exposure to androgens. A GnRH stimulation or human chorionic gonadotropin (hCG) test, done to assess the serum concentrations of testosterone, could be used to demonstrate the presence of testicular tissue. Because protocols vary among laboratories, the laboratory should be consulted for dosages and sampling times. Karyotyping can also be performed, although intersex animals may have normal karyotypes. Abnormal karyotypes have been found in bitches and queens with ovarian dysgenesis.

Induction of estrus may be tried in otherwise normal, healthy females if other diagnostic tests have failed to identify the cause of persistent anestrus. Exploratory celiotomy or laparoscopy, done to assess the gross appearance of the reproductive tract and to obtain biopsy specimens of the internal genitalia, should be considered only after all noninvasive diagnostic methods have been tried.

#### PROLONGED INTERESTROUS INTERVAL

Interestrous intervals of greater than 12 months in bitches and greater than 1 month in cycling queens are usually



**FIG 56-10**Diagnostic approach to female infertility. *B,* Bitch; *Q,* queen.

considered abnormal, although long interestrous intervals may also be a normal breed variation, as seen in the Basenji, Tibetan Mastiff, and Dingo dogs, which often cycle only once a year. Many of the causes of persistent anestrus, such as glucocorticoid administration in bitches and inadequate photoperiods in queens, may also cause a prolonged interestrous interval. Pregnancy, pseudopregnancy, and early embryonic death are causes of prolonged interestrous inter-

vals in queens but not in bitches. This difference is because the CL life span in bitches is 60 to 70 days, irrespective of pregnancy status. Lack of hiding places and irregular feeding times have been shown to disrupt normal cycles in cats (Pelican, 2006). Prolonged interestrous intervals may also occur with increasing age or may signify an underlying disorder. Silent or unobserved heats should also be considered. The diagnostic workup in animals with prolonged

interestrous intervals should include a thorough review of the estrus identification techniques used by the owner, identification of medications being administered to the animal, assessment of the overall metabolic health of the animal (i.e., CBC, biochemistry panel, urinalysis), and an evaluation of thyroid gland and adrenocortical function in bitches.

#### SHORT INTERESTROUS INTERVAL

Abnormally short interestrous intervals of less than 4 months are occasionally seen in bitches and are usually associated with infertility. Infertility in these animals presumably results from implantation failure because the endometrium has not recovered from the previous cycle, a process that takes 120 to 150 days, although ovulation failure may be involved. In some breeds, most notably the German Shepherd Dog, and in some individual animals, an interestrous interval of 4 to 4.5 months may be normal and may not interfere with fertility. Cystic ovarian follicles might cause frequent cycling (i.e., short interestrous interval) but most commonly are associated with persistent estrus. The administration of gonadotropins, prostaglandin F<sub>200</sub> prolactin antagonists, or estrogen can artificially shorten the interestrous interval. In most bitches, however, the cause of short interestrous intervals is not discovered.

A short interestrous interval must be differentiated from a *split heat* cycle in bitches. Split heats are characterized by normal proestrus that stops abruptly before progressing to estrus. Two to 4 weeks later, proestrus begins again and progresses through normal, fertile estrus. Split heats are a normal phenomenon that can occur in any bitch during any estrus. Split heats are seen most often in pubertal bitches that have normal proestrus and estrus during subsequent cycles. Rarely do split heats occur repeatedly in an individual bitch. Split heats do not cause infertility, except in the sense that the initial proestrus frustrates breeding management.

Additional diagnostic tests are often not performed in bitches with confirmed short interestrous intervals, although ovarian ultrasound would be reasonable. Another diagnostic consideration would be to monitor the changes in serum progesterone concentrations during estrus and diestrus to assess whether the short cycles may be related to ovulation failure. Administration of an androgen such as mibolerone or methyltestosterone to prevent estrus for at least 6 months has been considered, but there is little published evidence of efficacy. Even though estrus can easily be delayed with androgen treatment, affected bitches usually remain subfertile. Interrupting the short cycle by administering a progestin during proestrus has enabled 10 previously infertile bitches to conceive on the next cycle (Wanke, 2006). Previous interestrous intervals for the bitches were 2 to 4 months (mean 3.2 months). Treatment with megestrol acetate (2 mg/kg, orally) or clormadinone acetate (0.5 mg/kg, orally) for 8 days, beginning within the first 3 days of proestrus, stopped the cycle before ovulation. Progesterone concentrations remained at basal levels. The next cycles occurred 1.5 to 3.5 months (mean 2.7 months) after treatment and were fertile. Although subsequent cycles were not discussed in this report, breeding on the first estrus occurring after the discontinuation of therapy has previously been recommended because short interestrous intervals frequently resume. The role of genetics in this problem is not known.

# **ABNORMAL PROESTRUS AND ESTRUS**

The most common abnormalities of procestrus and estrus are refusal to allow mating, prolonged estrus, and abnormally short estrus. Females that are not in estrus refuse mating. An occasional bitch or queen exhibits partner preference by refusing to mate with one male but readily mating with another. Inexperienced and timid females may also be reluctant to breed. In bitches physical abnormalities of the vulva or vagina are common causes of refusal to mate (see Chapter 57). Physical abnormalities include vaginal strictures; congenital defects in the vulva and vagina; vaginal hyperplasia/ prolapse; and, rarely, vaginal neoplasia.

Vaginal cytologic studies should be performed to identify the present stage of the cycle (see Fig. 56-6). As just mentioned, females that are not in estrus will not accept mating. Digital palpation of the vulva, vestibule, and vagina in animals of adequate size can identify vaginal prolapse and most vaginal strictures and congenital defects. Vaginoscopy should be performed if digital palpation fails to identify a cause for the refusal to allow mating.

Vaginal strictures that are identified during anestrus should always be palpated again during estrus to determine their actual significance. Annular vaginal strictures are usually located immediately cranial to the external urethral orifice, at the anatomic junction between the vestibule and the vagina. The vestibulovaginal junction is normally the narrowest part of the posterior tract (see Fig. 56-7). During anestrus this normal narrowing may be mistaken for an annular stricture. The diameter of the vestibulovaginal junction normally increases significantly during proestrus and estrus, making differentiation from a true stricture easy at this stage of the cycle. Strictures of the vulva or vestibule usually do not change as dramatically during estrus. Similarly, normal vaginal examination findings during anestrus do not exclude the possibility of vaginal hyperplasia/prolapse, which occurs only at times of estrogenic stimulation, as a potential cause for reluctance to mate. Artificial insemination can be used to breed otherwise normal estrual females that refuse to mate as well as those with vaginal hyperplasia/prolapse. With the exception of vaginal hyperplasia/prolapse, physical abnormalities should be surgically corrected if the female is to remain in the breeding program. Surgery is best performed during anestrus. The heritability of congenital vaginal and vulvar anomalies is unknown.

# Prolonged or Persistent Estrus

Although procestrus and estrus each last an average of 9 days, proestrus lasting as long as 17 days and estrus lasting 21 days have been observed in normal, fertile bitches. Understandably, many owners become concerned if a season (proestrus plus estrus) lasts longer than 3 weeks. Nevertheless, a season is not considered abnormally long in bitches until it reaches



FIG 56-11 Cystic ovaries and uterus with cystic endometrial hyperplasia from a 2-year-old Mastiff in heat for 12 weeks.

35 to 40 days. In queens estrus lasting longer than 16 days is considered abnormal. This must not be confused with the normal, multiple cycles that occur in queens.

Prolonged proestrus/estrus is usually caused by functional follicular cysts (Fig. 56-11), which occur in intact ovaries and also in ovarian remnants in spayed bitches and queens. Ovarian neoplasia and exogenous estrogen administration may also cause persistent signs of estrus. Vaginal cytology should be performed to confirm that estrogenic stimulation is present and thus could reasonably be considered the cause of the behavioral and physical signs. Usually, the diagnosis of ovarian follicular cysts is based on the historic, physical, vaginal cytologic, and ultrasound findings. Serum concentrations of estrogen could also be determined. Because spontaneous regression of follicular cysts may occur, watchful waiting for 2 to 4 weeks is often the initial therapeutic approach. If clinical signs do not promptly resolve, treatment is indicated. Induction of ovulation can be attempted using GnRH (Cystorelin®; 2.2 µg/kg, adminstered intramuscularly q24h for 3 days); however, the results have been variable. If mature follicles are present and induced to ovulate, signs of estrus should resolve in 5 to 7 days. The cysts can be manually ruptured via laparoscopy or celiotomy. In cases of unilateral ovarian cysts, unilateral oophorectomy can be performed. Ovariohysterectomy should be considered for those females that fail to respond promptly to medical management for cystic ovaries because the prognosis for fertility is guarded and continued estrogenic stimulation may be harmful to the uterus and bone marrow. Ovarian neoplasia is uncommon in bitches and queens. Surgical excision is the treatment of choice. If exposure to exogenous estrogenic drugs is the cause of persistent signs of estrus, it should be discontinued.

#### **Short Estrus**

Abnormally short estrus of less than 3 days in bitches or less than 1 day in queens is most often the result of an error in observation or recognition of estrus. Females older than 6 to 8 years of age may experience erratic cycles, including short estrus. A split heat cycle should also be considered in bitches with an apparently short estrus. Short estrus may be normal in some animals. Methods of proestrus and estrus detection should be changed in females with a truly short estrus so that they can be bred at the appropriate time. This usually entails beginning vaginal cytologic studies or teasing with a stud well before the expected transition from proestrus to estrus and continuing this until the first day of estrus is identified. Combining this with ovulation timing, as determined by serum progesterone or LH concentrations, may be helpful in identifying the optimal time for insemination.

#### **NORMAL CYCLES**

Infertility in a female otherwise normal in all aspects of the reproductive cycle may result from improper breeding management; infertility in the male; abnormalities in the ovary, uterine tubes, uterus, or vagina; early embryonic death; or advancing age. A history of false pregnancy occurring after previous cycles strongly suggests that the hypothalamicpituitary-gonadal axis was intact during those cycles. Therefore the investigation should initially focus elsewhere. Conception rates and litter size are greatest and neonatal mortality is lowest in bitches (Beagles) between 2 and 3.5 years of age. Reproductive performance in queens is best between 1 and 6 years of age. After 5 years of age in Beagles and 6 years of age in queens, conception rates and litter size decline and neonatal mortality begins to increase. Because of this age-related decrease in fertility, an extensive diagnostic evaluation of older females may not be warranted.

The most common causes of infertility in females with normal estrous cycles are improper timing of insemination and poor semen quality. Because male fertility can be so easily evaluated (see Chapter 60), the male should be evaluated before an extensive diagnostic evaluation of the female is undertaken. A solid history that the male sired litters that were born shortly before and shortly after mating with the bitch in question would provide good circumstantial evidence against male infertility. Semen evaluation would provide information about the male's current status. The process of freezing and thawing canine semen substantially decreases its quality. Because the post-thaw life span may be only 24 hours and because its ability to transverse cervical mucus is so diminished, pregnancy rates using frozen semen are very poor unless ovulation timing and intrauterine, not intravaginal, insemination are used. Although the effects of chilling semen are far less deleterious, freshly ejaculated semen retains the best quality.

In well-managed colonies of normal dogs, conception rates of better than 90% are expected. A thorough history concerning breeding management, particularly how the owner determines when to breed, is imperative. Canine breeding management is discussed on p. 887. Feline breeding management is discussed on p. 889. A common practice for dog breeders is to simply begin breeding on a predetermined day after the onset of proestrus (commonly day 10) and

continue breeding every other day for as long as the bitch is receptive. This method works well for normal bitches that have a very typical cycle. However, if a particular bitch has a short proestrus, for example, day 10 may actually be at the end of estrus rather than at the beginning. In queens the frequency of mating during estrus is a more important determinant of ovulation, and thus conception, than is the specific day of the cycle on which mating occurs.

Vaginal cytology can be used to identify estrus. Obtaining the specimen for cytologic evaluation may induce ovulation in some estrous queens, but this is apparently not a common occurrence. Monitoring serum concentrations of LH or progesterone can be used to determine ovulation and the fertile period in bitches. It has been shown in bitches in artificial insemination (AI) programs that two inseminations, done 48 hours apart during the fertile period, improve pregnancy rates and increases the number of pups per litter compared with only one insemination. If the first insemination happens to occur late in the fertile period, the second is done 24 hours later. Unlike the situation in queens, breeding a bitch several times during the same day appears to offer no advantage over breeding a single time on a given day. Intrauterine insemination with fresh, chilled, or frozen-thawed semen increases pregnancy rates over vaginal insemination. Also, the mean litter size was larger with intrauterine AI than with vaginal Al.

After the female has been bred using optimal protocols and semen of excellent quality, it should be examined 20 to 30 days later to determine whether pregnancy has occurred. Pregnancy can be diagnosed on the basis of abdominal palpation, ultrasonographic findings, or by finding high serum concentrations of relaxin. Ultrasonography should be performed in animals found not pregnant because the ovaries and uterus can be evaluated for a potential cause. If the female is not pregnant, the serum progesterone concentration should be measured to determine if ovulation occurred. Low serum progesterone concentrations (less than 2 to 5 ng/ ml or approximately 6.4 to 16 nmol/L) suggest ovulation failure or premature luteolysis. The cause of ovulation failure may be an ovarian abnormality or, in the case of queens, inadequate coital stimulation. Premature luteolysis, or failure of the corpora lutea to maintain progesterone production, results in fetal resorption with no outward clinical signs when it occurs before day 35 of gestation. Premature luteolysis is rarely documented in bitches or queens; however, to differentiate ovulation failure from premature luteolysis, serum progesterone concentrations are serially determined using quantitative methods (e.g., RIA) from the time of proestrus through diestrus. Progesterone concentrations that never exceed 8 ng/ml (approximately 25 nmol/L) suggest ovulation failure, whereas premature luteolysis is reflected by a more rapid or earlier decline than normal from high postovulatory concentrations of progesterone. Hypothalamic or pituitary dysfunction would be unlikely causes of ovulation failure in the female that is otherwise cycling normally. More likely, hypothalamic or pituitary malfunction would be manifest as abnormal cycles.

When a female with normal cycles is known to have been bred appropriately during estrus to a male that is known to be fertile and when ovulation has been confirmed by the finding of elevated serum progesterone concentrations during diestrus, the hypothalamic-pituitary-gonadal axis is considered intact (see Fig. 56-4). Abnormalities in the vagina, uterus, uterine tubes, placenta, or the conceptus itself are then likely to be the source of the infertility. The diagnostic approach should begin with a review of the history to identify potential causes of early embryonic death. Special attention should be paid to infectious disease and medications administered to the female. Early embryonic death is difficult to confirm in bitches and queens, but in queens a prolonged interestrous interval provides a clue. Attempts to confirm pregnancy by ultrasound or measuring serum concentrations of relaxin can be done as early as day 14 to 20, although false-negative results are understandably common at that stage.

Infectious agents are an important cause of early embryonic death. Although many agents are capable of causing placentitis or fetal death, B. canis in bitches and calici and herpes viruses in queens are the foremost such agents. In lieu of cultures of specimens from the uterine lumen, cultures of the cranial vagina should be performed. Some clinicians recommend that cultures be obtained during estrus because the cervix is open at that time and fluid in the cranial vagina may have originated from the uterus. Bacterial infections should be treated appropriately before breeding. The uterus may be incapable of supporting implantation or pregnancy because of disorders such as bacterial endometritis or cystic endometrial hyperplasia. Ultrasound of the reproductive tract is indicated. Vaginal lesions can easily be excluded as the cause of infertility by vaginoscopy and vaginal cytology. The potential teratogenic or abortifacient effects of medications should always be considered. Many commonly used medications, such as glucocorticoids and certain antibiotics, also cause embryonic death. In addition, some congenital fetal anomalies cause early embryonic death because they are incompatible with continued survival.

The presence of antisperm antibodies in the female has not yet been documented as a cause of infertility in dogs or cats. However, were they to occur, breeding with a different male could circumvent the problem. Finally, exploratory celiotomy can be performed during anestrus to visualize the reproductive tract, assess the patency of the uterus and uterine tubes, obtain uterine specimens for culture, and procure full-thickness uterine biopsy specimens for histologic assessment.

# ESTRUS SUPPRESSION, CONTRACEPTION, AND POPULATION CONTROL

# **SURGICAL METHODS**

In the United States and Canada ovariohysterectomy and castration are the most common methods of population

control for dogs and cats. They are permanent and relatively expensive, invasive procedures. Ovariohysterectomy can be accomplished by midline or flank approaches or via laparoscopy. Laparoscopy has also been used for castration of cryptorchid testicles. Some clinicians have recommended ovariectomy over ovariohysterectomy, although this has not been widely accepted among veterinarians in the United States. Ovariohysterectomy has traditionally been recommended at 5 to 8 months of age, just before the animal reaches puberty. Doing so dramatically reduces the risk that the animal will develop mammary cancer in the future, in addition to preventing estrus and unwanted pregnancy. To reduce the number of unwanted (i.e., relinquished by their owners) and stray animals euthanized at animal shelters, many shelters mandate surgical sterilization as part of the adoption agreement. Because postadoption compliance with sterilization agreements has universally been poor, preadoption "early spay-neuter" policies at 6 to 8 weeks of age have been advocated. Safe and effective anesthetic and surgical techniques have been developed. Several studies have shown that the physical and behavioral traits of animals neutered at 7 weeks of age are the same as those in animals neutered at the more conventional age of 7 months. However, there is an increased rate of urinary incontinence in female dogs spayed at 6 to 8 weeks of age compared with those spayed at 6 to 8 months. Whereas the risks associated with early spayneuter of male dogs and of both male and female cats are minimal, it may be prudent to delay spaying female dogs until they are older. Gonadectomy at any age results in decreased metabolic rate and decreased caloric requirements, irrespective of any change in physical activity. It has also been reported that food intake actually increases after neutering in male and female cats fed ad libitum. Neutering has been shown to cause hyperleptinemia in male cats, but not female cats, after neutering. Unless caloric intake is diminished to match the changed metabolic rate, animals will gain weight after gonadectomy. Gonadectomized animals have delayed physeal closure, and less developed genitalia and secondary sex characteristics than do age-matched, sexually intact controls. Tubal ligation and vasectomy can be used to prevent pregnancy in dogs and cats without circumventing the physical and behavioral changes associated with sexual maturation. Owners may or may not consider this desirable.

# NON-SURGICAL METHODS FOR CONTRACEPTION OR STERILIZATION

Less expensive, permanent, nonsurgical methods of sterilization would be ideal for preadoption programs at humane societies and animal shelters and for large-scale application in trap-neuter-release programs to control feral populations. The injection of sclerosing agents into the testis, epididymis, or ductus deferens has been investigated in dogs and cats. These agents have included various concentrations of zinc, formalin, chlorhexidine in DMSO, ethanol, silver nitrate, potassium permagnate, Freund's Complete Adjuvant, BCG, methallibure, dexamethasone, metopiron, niridazol, α-chlorohydrine, and danazol. Treated animals may remain

fertile for 6 to 8 weeks after treatment. Some animals never become sterile, whereas in others the effects are transient. There appears to be some species variation as well because intratesticular 70% glycerol was ineffective in dogs, whereas it has consistently resulted in azoospermia in monkeys, rabbits, rats, and hamsters. Some studies have reported minimal signs of discomfort. Others have reported swelling, scrotal ulceration and mutilation, local granulomatous reactions, vomiting, diarrhea, leukocytosis, and lethargy. A zinc gluconate solution (Neutersol®; Addison Biological Laboratory) for intratesticular injection is marketed for chemical castration of puppies between 3 and 10 months of age. At this time there is no published evidence that the use of sclerosing agents has resulted in lifelong sterility in pet dogs or cats or that there has been an impact on control of feral populations.

The concept of immunizing animals against GnRH, LH, LH receptors, sperm antigens, and the zona pellucida of oocytes has appeal for both permanent sterilization and temporary contraception. Because GnRH and LH control gonadal function, blocking their effects would theoretically suppress estrus cycles and ovulation in females, spermatogenesis in males, and sexual behavior in males and females. These effects might be maintained permanently or temporarily, depending on the duration of adequate antibody titers. GnRH is highly conserved across species and therefore is poorly immunogenic unless conjugated with other molecules. A GnRH vaccine (Improvac®; CSL Animal Health) is available in Australia for use in mares. An antigonadotropin releasing factor (GnRF) product (Canine Gonadotropin Releasing Factor Immunotherapeutic®; Pfizer) is marketed in the United States for treatment of benign prostatic hyperplasia in dogs. Although not marketed for these effects, it does cause the testes to shrink and serum testosterone concentrations to decline, both of which would be deleterious to spermatogenesis. GnRH has also been conjugated with cytotoxic agents designed to destroy the GnRH receptors. Although this markedly suppressed reproductive activity in peripubertal male dogs, the response was variable. Induction of antibodies against LH and LH receptors results in impaired reproduction; however, the responses have been so variable that a consistent vaccination protocol has not been established for dogs or cats. Bitches and queens have resumed normal cycling after antibody titers declined. Attempts to immunize animals against sperm antigen have not had satisfactory results for sterilization or contraception. The zona pellucida (ZP) is the acellular coating around ova, and vaccination with porcine ZP has been found to consistently produce high antiZP titers and prevent conception in bitches. Significant ovarian abnormalities also develop, including ovarian cysts of various types and prolonged proestrus/ estrus. Vaccination of queens against ZP has not resulted in contraception. An antiporcine ZP vaccine (SpayVac®; Immuno Vaccine Technologies, Nova Scotia) is commercially available for immunocontraception in some captive wild species.

Intravaginal spermacides have not yet been developed for use in bitches or queens. An intravaginal mechanical barrier was marketed for use in bitches, but the failure rate was high. An intrauterine contraceptive device is available for bitches (Biotumer, Argentina). Although it was quite effective in a small clinical trial (Volpe, 2001), it is somewhat impractical because of the difficulty in transcervical placement. High intensity ultrasound suppresses spermatogenesis when applied to the testes and causes luminal occlusion when applied to the epididymides and ductus deferentia in dogs and cats. However, skin burns occur in approximately 20% of treated animals. Bisdiamines are amebicidal drugs that have been found to cause spermatogenic arrest in all species studied thus far, including dogs and cats. They have generated great interest for contraception in zoo animals because, when administered daily in food, they cause spermatogenic arrest before the spermatid stage but spermatogonia are preserved. Therefore the effects are reversible. Side effects in dogs and men have been only slight weight loss and slight decrease in red blood cell count. In cats there was no change in red blood cell counts, but testosterone concentrations declined during treatment. The drug must be administered daily to be effective. Females must not be exposed to bisdiamines because they are highly teratogenic.

#### CONTRACEPTION

Contraception may be defined as a reversible method of blocking fertility. Contraception is particularly desirable for animals that eventually will be bred but for which estrus will interfere with their work (e.g., racing, hunting) or show career. Progestins and androgens can inhibit the release or synthesis of gonadotropins in dogs and cats and thereby prevent estrus. GnRH analogues reversibly inhibit reproductive function in males and females by downregulating LH and FSH receptors, thereby suppressing the pituitary-gonadal axis.

# **Progestins**

Megestrol acetate (Ovaban®; Pfizer) is the only progestin approved for estrus control in bitches in the United States. It is not labeled for use in cats. It is intended for short-term (2 years), temporary use. In some European countries oral and injectable progestins such as medroxyprogesterone acetate (MPA; 3 mg/kg, administered intramuscularly every 5 to 6 months) and proligestone are commonly used to prevent estrus. Progestins are most reliable in preventing estrus when treatment is initiated during anestrus and are less reliable if initiated during early proestrus. The synthetic progestin levonorgestrel (Norplant®; Wyeth-Ayerst) is a slow-release, subdermal implant. It is effective in suppressing estrus for 12 months in cats, with no adverse effects except the development of cystic endometrial hyperplasia. The return to normal cycling after discontinuing progestin therapy is variable but typically is within 2 and 9 months. Progestins have many dose-dependent undesirable effects that commonly occur at therapeutic doses. Progestins routinely cause cystic endometrial hyperplasia, which may predispose the animal to the development of pyometra. Twelve weeks after initiating MPA treatment at 10 mg/kg subcutaneously, every 3 weeks, there was atrophy of the endometrium and dramatic reduction in estrogen and progesterone receptors. However, by 24 weeks, most uterine cell types had escaped progestin downregulation, estrogen and progesterone receptors had returned to normal, and cysts of endometrial glands had developed (De Bosschere, 2002). Progestins are also associated with mammary hyperplasia and an increased incidence of mammary tumors. When progestin therapy is discontinued, signs of false pregnancy may develop (see Chapter 58). Other adverse effects in bitches and queens include diabetes mellitus, acromegaly, and adrenocortical suppression. Conversely, some progestins (MPA and proligestone) act as glucocorticoid agonists in the bitch, and longterm treatment with high doses may result in iatrogenic hyperadrenocorticism, including steroid hepatopathy. Alopecia, thinning of the skin, and discoloration of the hair at the site of progestin injection have also been observed. For these reasons, the benefit of progestins for estrus suppression should be carefully weighed against the risks. Medroxyprogesterone is used for the treatment of benign prostatic hyperplasia in dogs (see Chapter 62) with no apparent adverse effects on semen quality. At higher doses (20 mg/kg), MPA decreases sperm output and motility and increases morphologic abnormalities.

# **Androgens**

Mibolerone (Cheque Drops®; Pfizer) was the only androgen approved for estrus suppression in bitches in the United States. The dose varied according to body weight and breed. Daily doses of 50 µg were required to suppress estrus in queens, but doses of 60 µg caused heptotoxicity. Although not labeled for this use, various forms of testosterone (testosterone propionate, 110 mg, administered intramuscularly or subcutaneously, once weekly; methyltestosterone, 25 to 50 mg, administered orally, twice weekly) are routinely administered to Greyhound bitches during training and racing. Prolonged anestrus occurs in some of these bitches after androgen therapy is discontinued. Adverse effects of androgens are clitoral hypertrophy (sometimes with permanent ossification), mucopurulent vulvar discharge, and vaginitis. Liver enzyme activity may also be increased. These effects are usually reversible after androgens are discontinued, but they may persist for months to years. Irreversible masculinization of the female fetuses occurs when androgens are administered to pregnant females. Additional androgenic effects include thickening of the skin on the neck of queens and an apparent increase in muscle mass and aggressiveness in bitches. Subcutaneous administration of 0.6 mg/kg testosterone propionate to dogs caused marked decline in sperm motility that persisted for 3 months. Oral administration of 50 mg of methyltestosterone for 1 month decreased sperm output. Chronic administration of the synthetic testosterone danazol causes azoospermia in dogs.

#### **GnRH Agonists**

The GnRH agonist deslorelin has been shown to safely and effectively suppress reproductive function for up to 2 years

in adult male and female dogs and cats when administered as a slow-release subcutaneous implant. (Ovuplant®, Fort Dodge; Suprelorin®; Peptech Animal Health). Depending on the age of the bitch and the stage of the cycle at which a GnRH agonist is implanted, it can initially induce an estrus cycle. This unwanted effect can be overcome by the simultaneous short-term administration of a progestin such as megestrol acetate. After an initial stimulatory effect on the pituitary gonadotropins, GnRH agonists suppress further LH and FSH release by downregulation of receptors. Other GnRH agonists, nafarelin, leuprolide, and buserelin, are also effective contraceptives in bitches and dogs. A formulation of nafarelin safely and effectively delayed puberty when administered to prepubertal bitches (mean age 5 months) as a slow-release subcutaneous implant for the duration of the 1-year study. Spontaneous cycling occurred 1 to 13 months after the implants were removed. The implants were difficult to find and remove from two obese bitches.

# OVARIAN REMNANT SYNDROME

Occasionally, queens and bitches resume cycling or continue to exhibit behavioral and physical signs of estrus after oophorectomy. This may happen weeks or as long as 5 years after oophorectomy. The signs may be cyclic in nature, or there may be persistent signs of hyperestrogenism, including alopecia, hyperpigmentation, and lichenification. The cause is remnant ovarian tissue that has regained folliculogenesis and estrogen production. The presence of high concentrations of estrogen can be detected using vaginal cytology to identify cornification of epithelial cells (see Fig. 56-6). The history should be reviewed to ensure that the patient is not being exposed to exogenous estrogens (e.g., agents prescribed to treat urinary incontinence in the patient) or estrogen-containing creams, contraceptives, or hormone replacement therapy used by owner. In the absence of exogenous estrogens, the findings of clinical signs typical of estrus, along with vaginal cytology consistent with estrus, confirm the presence of ovarian remnants and justify a recommendation for exploratory celiotomy to find and remove the ovarian remnants. If additional confirmation of the ovarian remnant syndrome is desired before exploratory surgery, the remnant ovary's ability to ovulate and produce progesterone can be evaluated. Measuring serum concentrations of progesterone 5 to 7 days after expected ovulation achieves this goal. In bitches progesterone increases during heat, coincident with the LH surge, and remains elevated for about 60 days thereafter. Therefore progesterone could be measured while the bitch is showing the clinical signs of heat or for several weeks thereafter. Queens generally are considered to be induced to ovulate by coital stimulation. However, many also ovulate spontaneously. Progesterone remains elevated for only 30 to 40 days after ovulation in nonpregnant queens. Therefore progesterone is measured a week or two after the signs of heat in queens. Progesterone concentrations greater than 2 ng/ml (6.4 nmol/L) are indicative of spontaneous ovulation and the presence of CL in the ovarian remnants. The clinician should keep in mind that ovarian remnants may not be "cycling" in a normal manner and ovulation may not occur. Some ovarian remnants develop cystic follicles that produce estrogen but do not ovulate. The finding of high progesterone confirms the presence of ovarian remnant, but low progesterone does not exclude it. Another approach is to attempt to induce ovulation while the female is in heat by administering hCG (10 IU/kg, intramuscularly, in bitches; 250 IU/queen, intramuscularly) or GnRH (0.5 µg/kg, intramuscularly, in bitches; 25 µg/cat, intramuscularly). Approximately 5 to 7 days later the serum progesterone concentration should exceed 2 ng/ml if responsive ovarian tissue is present. The finding of low serum concentrations of LH indicates the presence of ovarian tissue. However, it is possible that exogenous estrogens could also suppress LH.

Ovarian remnants are often bilateral. They are typically found in the usual anatomic location for ovaries, not in aberrant or ectopic places. The cause of ovarian remnant syndrome is evidently the surgical technique. Treatment consists in the surgical removal of the ovarian remnants. Ovarian remnants are often small, despite the magnitude of the clinical signs they cause. They may be obscured by periovarian fat, especially in bitches. Some veterinarians have suggested that ovarian remnants may be easier to identify if follicles (i.e., when the female is in heat) or CL (i.e., shortly after ovulation) are present rather than during the interestrous period (i.e., anestrus). However, in our experience, the most important determinant of success is adequate surgical exposure and dissection.

# OVARIAN NEOPLASIA

Ovarian neoplasia is rare in bitches and queens. Granulosa cell tumors are reported to occur in ovarian remnants as well as in intact females (Fig. 56-12). Bitches with estrogen-producing ovarian tumors may have clinical signs of estrus, bone marrow toxicity, dermatologic changes, or a combination of these. Estrogen-producing ovarian tumors would not be expected to respond to exogenous hCG or GnRH administration. Bitches with progesterone-producing granulosa cell tumors may show mammary gland development and may have cystic endometrial hyperplasia.

# INDUCTION OF ESTRUS AND OVULATION

Estrus induction has been attempted in bitches in clinical settings to shorten the normal interestrous interval, to treat primary and secondary anestrus, and to time pregnancy and parturition for the owners' convenience. In research settings estrus induction has been used for in vitro fertilization (IVF) and to synchronize estrus for embryo transfer (ET). Although some estrus-induction protocols are associated with superovulation, as revealed by examination of ovarian follicles, the

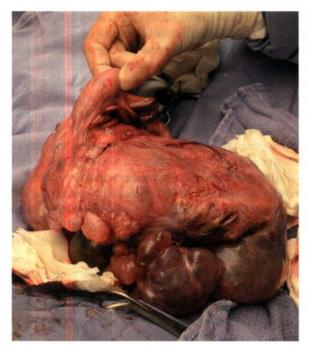


FIG 56-12
Ovarian papillary cystadenocarcinoma in an 8-year-old mixed-breed dog weighing 35 lb, in heat 6 weeks ago. (Courtesy Dr. Jennifer Ellis, Elkhart, Ind.)

superovulation is apparently not reflected in increased litter size. Induction of ovulation may be indicated for females with ovulation failure as shown by low diestrous serum concentrations of progesterone or for those with persistent estrus caused by ovarian follicular cysts.

#### THE QUEEN

The photoperiod can be manipulated to induce estrus in queens. Continuous exposure to 12 to 14 hours of light of at least 50 foot-candles and exposure to 10 to 12 hours of dark per day causes normal, mature queens to begin cycling within 4 to 8 weeks. Housing anestrous queens with cycling queens also helps to induce estrus. If the hormonal induction of estrus is to be attempted, the queen should first be exposed for several months to a minimum of 12 hours of light per 24 hours. Induction of ovulation may be indicated for cycling queens in AI or IVF/ET programs or to induce pseudopregnancy, which would temporarily prolong the interestrous interval when frequent cycles are troubling the owners. The intramuscular administration of 250 IU of hCG or 25 | g of GnRH (Cystorelin; Ceva) on the first 2 days of estrus is recommended, although a single 25-µg dose of GnRH is known to cause an LH surge in normal cats. Probing the vagina with a smooth rod such as a thermometer or with a cotton swab four to eight times, at 5- to 20-minute intervals, may also stimulate an LH surge in normal cycling queens. The probing need last only 2 to 5 seconds.

Estrus induction has primarily involved using domestic cats as models for AI and IVF/ET in endangered wild felids.

The most common hormones used to induce estrus (i.e., folliculogenesis) in cats are porcine FSH and equine chorionic gonadotropin (eCG). A disadvantage of pFSH is the need for daily administration until the onset of estrus. Because of its longer half-life, a single injection of eCG (100 IU, intramuscularly) is often sufficient. Ovulation is then induced with LH (hCG; 75, 100, or 250 IU, administered intramuscularly or intravenously, depending on the formulation), or mating with a tomcat. A commonly used protocol for artificial insemination regimens is eCG followed by hCG 80 to 84 hours later. Protocols using GnRH for estrus induction have also been successful, but to date, pregnancy rates have been lower. Although there is much variation in response to estrus induction protocols among feline species, a common problem is hyperstimulation of the ovaries. This has resulted in excessive or prolonged estrogen production, premature or prolonged progesterone production, or premature luteolysis, all of which disrupt rather than enhance reproduction. It has been shown in cattle that follicular cysts develop following luteal phases with inadequate progesterone levels. Therefore the use of progestins before gonadotropins to help prevent ovarian hyperstimulation is being investigated (Pelican, 2006).

# THE BITCH

Many drugs have been used to induce estrus—in other words, to shorten the interestrual interval—in bitches. Prostaglandin  $F_{2\alpha}$ , which is used to treat pyometra, causes luteolysis and decreased progesterone production by the CL. This shortens the normally long diestrous period and thereby shortens the interestrual interval by 1 to 2 months.

The mechanisms by which the dopamine agonists cabergoline and bromocriptine induce estrus are multifactorial. One mechanism is by suppression of prolactin, which is luteotropic. Suppressing luteal function decreases progesterone, shortens diestrus, and increases LH pulsatility in bitches. However, this is not the sole explanation because metergoline, a seratonin antagonist that also decreases prolactin, does not induce estrus in bitches. Furthermore, even at low doses that do not suppress prolactin nor shorten diestrus, bromocriptine significantly shortens the interestrous interval. Bromocriptine (Lactafal®, Eurovet), given orally q12h at doses of 5, 20 and 50 µg, beginning in mid-diestrus until the onset of the next cycle, resulted in mean interestrual intervals of  $136 \pm 16$  days,  $96 \pm 6$  days, and  $92 \pm 11$  days, respectively, compared with untreated controls' mean interval of 216  $\pm$  9 days (Beijerink et al., 2003). The higher doses suppressed prolactin and progesterone, whereas the low dose did not. Other researchers have reported that some bromocriptineinduced cycles are not fertile, despite hormonal variations similar to those in normal cycles. Cabergoline (Galastop®, Ceva Vetem; Dostinex®, Pfizer) at a dosage of 5 µg/kg orally, q24h, through the first 2 days of proestrus has induced fertile estrus in bitches with primary and secondary anestrus. The duration of treatment ranged from 4 to 34 days, with a mean of 16 days. Other researchers have suggested that continuing

treatment through the first 4 to 5 days of proestrus is important for success.

GnRH agonists, administered as slow-release implants, induce estrus in bitches. The effectiveness of estrus induction and the fertility of the induced cycle are dose dependent and age dependent and vary according to the stage of the cycle during which the drug is administered and perhaps the anatomic location of the implant. These variations are apparently the result of competing upregulation and downregulation of LH release. The GnRH agonist deslorelin has been studied for both estrus induction and estrus suppression in bitches. High doses induced fertile estrus, but abortions occurred during the ensuing diestrus. Lower doses of 1.05 mg or 2.1 mg deslorelin (Ovuplant®, Fort Dodge) implanted in Beagle bitches beneath the vestibular submucosa in the ventral commissure of the vulva reliably induced proestrus within 3 to 5 days of administration, and the LH surge occurred 9 to 17 days later (Volkmann et al., 2006). All the bitches implanted during anestrus ovulated, and 69% became pregnant when bred to the same dogs as were the untreated controls. All the untreated controls also ovulated, and 67% became pregnant. However, although bitches implanted during diestrus also came into estrus and experienced an LH surge, only 69% ovulated and the pregnancy rate was only 15%. Furthermore, 15% of those treated in diestrus developed pyometra during the diestrus after the induced estrus.

Induction of ovulation might be indicated for cycling bitches in which ovulation is failing to occur or bitches with follicular ovarian cysts. Potential agents include hCG (22 IU/kg, intramuscularly) and GnRH (50 to 100 µg, intramuscularly; or 2.2 µg/kg, intramuscularly GnRH; Cystorelin®, Ceva). It has been recommended that hCG and GnRH be given on the first day of estrus, as determined by the behavior of the bitch and vaginal cytology. Success is confirmed by the finding of a serum progesterone concentration of greater than 8 ng/ml in early diestrus. For the treatment of follicular cystic ovarian disease in the bitch, 2.2 µg/kg of GnRH is administered intramuscularly for 3 days. However, the results of this treatment have been disappointing.

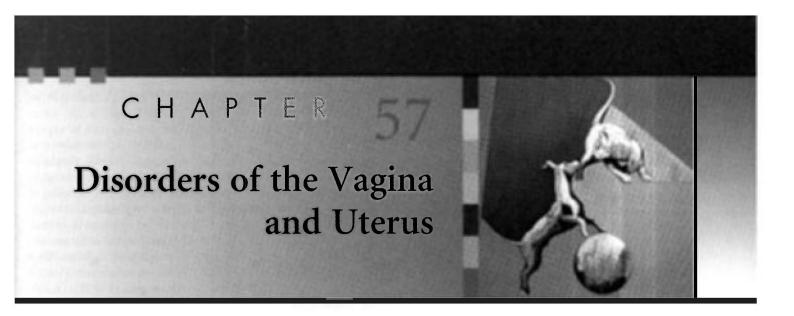
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# 910 PART VIII Reproductive System Disorders

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# CHAPTER OUTLINE

DIAGNOSTIC APPROACH TO VULVAR DISCHARGE

Hemorrhagic Vulvar Discharge

Mucoid Vulvar Discharge

Exudate

Abnormal Cells

ANOMALIES OF THE VULVA, VESTIBULE, AND

VAGINA

CLITORAL HYPERTROPHY

**VAGINITIS** 

Prepubertal Bitch

Mature Bitch

Chronic, Nonresponsive Vaginitis

**NEOPLASIA** 

VAGINAL HYPERPLASIA/PROLAPSE

DISORDERS OF THE UTERUS

CYSTIC ENDOMETRIAL HYPERPLASIA, MUCOMETRA,

and pyometra

Cystic Endometrial Hyperplasia

Mucometra

Pyometra

# DIAGNOSTIC APPROACH TO VULVAR DISCHARGE

Vulvar discharge is commonly found in bitches with disorders of the reproductive tract and, less commonly, disorders of the urinary tract. Vulvar discharge is also normal during proestrus, estrus, and the postpartum period. Vulvar discharge is uncommonly observed in queens. Determining the significance of the discharge depends on the stage of the reproductive cycle, the cellular composition of the discharge, and the source of the discharge. The diagnostic approach includes a thorough history-taking, physical examination, vaginal cytology, and vaginoscopy. When taking the history, the clinician should establish the stage of the reproductive cycle and the overall health of the bitch. The complete physi-

cal examination includes inspection of the discharge and vulva and palpation of the reproductive tract. Disorders of the vulva, vestibule, or vagina rarely cause signs other than vulvar discharge, licking of the vulva, and/or pollakiuria. Physical abnormalities are usually confined to these areas. In contrast, disorders of the uterus frequently result in systemic signs of illness in addition to a vulvar discharge. Historical findings such as malaise, weight loss, vomiting, or polydipsia-polyuria are suggestive of systemic illness, as are physical findings such as fever and dehydration. They deserve prompt attention.

The character of the vulvar discharge is determined by visual inspection and vaginal cytology (Box 57-1). Some characteristics, such as meconium, urine, and uteroverdin, can be confirmed by visual inspection. Uteroverdin is the dark green heme pigment normally found in the canine placenta. In the cat placental blood is red-brown in color. Its presence in a vulvar discharge indicates that placental separation has occurred. This is normal during stage II of parturition and during the first few hours postpartum, but it is abnormal at any other time. Sometimes, inflammation of the lower urinary tract or vestibule will cause dribbling of urine, which may be described by owners as a discharge. Meconium is the bright yellow fetal fecal material. Its presence indicates extreme fetal distress.

There are two important aspects of evaluating vaginal cytology. The first is examination of the vaginal epithelial cells for the maturation and cornification induced by estrogen (see Chapter 56 and Fig. 56-6). The second is identification of other cell types and mucus. The source of the vulvar discharge is confirmed by physical examination of the vulva and endoscopic examination of the vestibule and vagina. If a uterine source of the discharge is suspected, abdominal radiography and/or ultrasonography of the uterus should also be performed. Further diagnostic tests may be indicated once the origin and probable cause of the discharge have been established.

# HEMORRHAGIC VULVAR DISCHARGE

Red blood cells (RBCs) are commonly found in normal and abnormal vulvar discharges. The other types of cells that are



Differential Diagnoses for Vulvar Discharge Based on Predominant Cytologic Characteristics

#### Cornified (Mature or Superficial) Epithelial Cells

Normal proestrus Normal estrus Ovarian remnant syndrome Abnormal source of estrogen

Exogenous

- · Patient's estrogen for urinary incontinence
- Owner's estrogen-containing cream, hormone replacement, birth control
- Soy phytoestrogens in diet (?)

Ovarian follicular cyst

Ovarian neoplasia

Contamination with squamous epithelium Skin or clitoris

#### **Peripheral Blood**

Subinvoluted placental sites Uterine or vaginal neoplasia Trauma to reproductive tract Uterine torsion Coagulopathies

#### Mucus

Normal late diestrus or late pregnancy Normal lochia Mucometra Androgenic stimulation Idiopathic (?)

#### **Exudate**

Cellular debris Normal lochia Abortion Neutrophils

Nonseptic (no organisms seen)

- Normal first day of diestrus
- Vaginitis
- Metritis or pyometra (possible but unlikely)

Septic (organisms seen)

- Vaginitis
- Metritis
- Pyometra
- Abortion

also present, particularly vaginal epithelial cells and white blood cells, determine their significance. In addition to the plentiful RBCs, the predominant cytologic finding during normal proestrus and estrus is numerous mature (cornified) superficial vaginal epithelial cells, indicating an estrogenic influence. White blood cells (WBCs) and extracellular bacteria may also be present. Ovarian remnant syndrome, exogenous estrogen, and the pathologic production of estrogens by ovarian follicular cysts or ovarian neoplasia can cause similar cytologic findings.

When RBCs are the predominant cytologic finding in the absence of cornified vaginal epithelial cells (i.e., no estrogenic influence), a cause for hemorrhage, such as vaginal laceration, uterine and vaginal neoplasia, subinvoluted placental sites, uterine torsion, and coagulopathies, should be sought. Vaginal laceration or other trauma to the reproductive tract is uncommon but may occur during breeding or as a result of vaginoscopy or obstetric procedures. Although bleeding from the vulva is certainly not common in animals with coagulation defects, it has been observed as the sole site of bleeding in some bitches with coagulopathies. When RBCs are accompanied by WBCs as the predominant cytologic abnormality, especially when the number of WBCs exceeds that expected in peripheral blood, a cause of inflammation (WBCs) rather than of hemorrhage (RBCs) should be sought.

#### MUCOID VULVAR DISCHARGE

Mucus is the predominant component of the normal postpartum discharge, lochia (see Chapter 59). It may also be present during normal late pregnancy and possibly in small amounts during the nonpregnant luteal phase. Cervicitis and mucometra can cause a mucoid vulvar discharge. In rare instances no apparent cause can be found in some bitches with small amounts of mucous discharge.

#### **EXUDATE**

Cellular debris is often the predominant component of the discharge that accompanies abortion and also of the discharge that accompanies the metritis associated with retained fetal or placental tissue. Some debris is also present in lochia.

# **Purulent Vulvar Discharge**

Purulent and mucopurulent vulvar discharges are characterized by a predominance of polymorphonuclear cells (PMNs), with or without mucus. When bacteria are also present, the exudate is referred to as *septic*. Large numbers of PMNs without signs of degeneration or sepsis are often found during the first day or two of diestrus (see Chapter 56). This normal diestrual return of WBCs to the vaginal smear can be differentiated from inflammation of the reproductive tract by the absence of clinical signs, the temporal correlation with recent estrus, and the prompt disappearance of WBCs within 48 hours of the onset of diestrus.

A nonseptic exudate is often found in prepubertal bitches with vaginitis. Androgenic stimulation (exogenous testosterone or an intersex condition) can also cause a nonseptic inflammation. Other causes of nonseptic and septic vulvar discharges include vulvitis, vaginitis, pyometra, metritis (see Chapter 59), abortion (see Chapter 58), and a uterine stump granuloma or abscess.

### **ABNORMAL CELLS**

The characteristic appearance of endometrial cells easily distinguishes them from other cells seen on vaginal cytologic preparations. They are columnar and have a basal nucleus

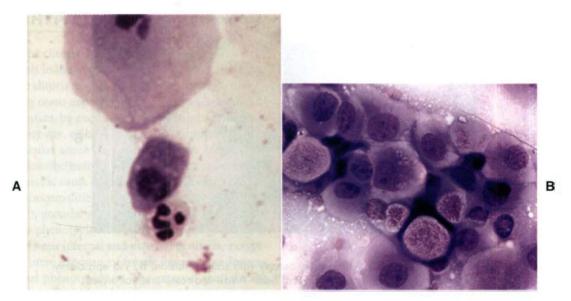


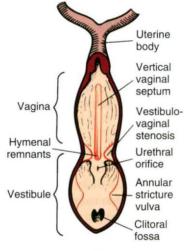
FIG 57-1
Abnormal findings on vaginal cytology. A, Canine endometrial cell with superficial vaginal epithelial cell and neutrophil. B, Transitional cell carcinoma from a bitch with hemorrhagic vaginal discharge.

and foamy cytoplasm (Fig. 57-1). The presence of endometrial cells indicates uterine involvement. They may be found in animals with cystic endometrial hyperplasia, even in the absence of an overt vulvar discharge, or, less commonly, in lochia and in animals with metritis. Transmissible venereal tumors and transitional cell carcinomas readily exfoliate, and neoplastic cells may be found on vaginal cytologic preparations (see Fig 57-1). Leiomyomas do not readily exfoliate.

# ANOMALIES OF THE VULVA, VESTIBULE, AND VAGINA

The müllerian ducts are the embryologic origin of the uterine tubes, uterus, and vagina. The vestibule, urethra, and urinary bladder develop from the urogenital sinus. Thus the vestibulovaginal junction is immediately cranial to the urethral orifice. The genital folds also form part of the vestibule (Fig. 57-2). The fusion of the Müllerian ducts with the urogenital sinus forms the hymen, which is composed of two epithelial surfaces separated by a thin layer of mesoderm. In bitches the hymen reportedly disappears before birth. The genital tubercle gives rise to the clitoris, and the genital swellings become the labia (vulva).

The abnormal formation or disappearance of the hymen can result in a vertical band of tissue or in an annular stricture at the vestibulovaginal junction. The latter condition has also been referred to as *vestibulovaginal stenosis*. Abnormal or incomplete fusion of the paired müllerian ducts can result in the formation of an elongated vertical septum that bisects the vagina (Fig. 57-3) or in the formation of a vaginal diverticulum (pouch). Vaginal diverticula are uncommon.



**ANOMALOUS STRUCTURES** 

FIG 57-2
Anatomic location of normal structures and common congenital anomalies of the canine vagina and vulva. (Redrawn from Miller ME et al, editors: Anatomy of the

dog, Philadelphia, 1964, WB Saunders.)

Complete duplication of parts of the urogenital tract, including a true double vagina, has been reported, but this is extremely rare. Abnormal fusion of the genital folds with the genital swellings can result in the formation of strictures within the vestibule and vagina. With the exception of abnormalities of the vulva and vestibule, the common congenital anomalies are located immediately cranial to the external urethral orifice. Hypoplasia or agenesis of parts of the reproductive tract also occurs. All these congenital anomalies of



FIG 57-3
Vaginal septa in two bitches. **A,** Via vaginoscopy with saline infusion. **B,** Via episiotomy. Spay hook used to bring septum into surgical field. *Arrow* indicates urethral orifice.

the vagina and vulva have been found in bitches, but they are apparently extremely rare in queens.

Growth and maturation of the vulva and vagina depend on the ovarian hormones. When ovariectomy is performed before puberty, the reproductive tract remains in its infantile or juvenile stage of development. When the ovaries are removed after puberty, some atrophy occurs, but the reproductive tract does not return to its prepubertal size. Depending on the smallness of the vulva and the overall perineal conformation, the vulva may be recessed in the perineal skin. A recessed vulva could be congenital or acquired. In some obese individuals rolls of perineal fat cover the vulva.

#### **Clinical Features**

Anomalies of the vulva and vagina often cause no clinical signs, or they may be associated with perivulvar dermatitis, recurrent urinary tract infections, chronic vaginitis, or refusal to mate. Vulvar-vaginal anomalies are often recognized only because the female refuses to mate or because the male dismounts without being able to achieve intromission. Occasionally, vulvar-vaginal anomalies are associated with urinary incontinence. This may be due to urine pooling anterior to the lesion, or there may be other, concurrent congenital anomalies in the urogenital tract, such as ectopic ureters.

#### Diagnosis

Anomalies of the vulva and vagina are easily identified by physical examination and digital palpation. Most anomalies involve the caudal aspect of the tract, from the vestibulovaginal junction outward, and are easily reachable. Vaginoscopy (see Chapter 56) is very useful for evaluating the vestibule and vagina and may be combined with urethrocystoscopy in cases with urinary incontinence. Vaginography (see Chapter 56) can also be performed, but care must be taken with the plane of anesthesia, positioning of the patient, and interpretation of the findings. The vestibulovaginal junction is normally so narrow during anestrus, especially in pubescent bitches, that it may be mistaken for a stricture or

stenosis. Furthermore, contraction of the constrictor vestibuli muscle, which may occur during manipulation of the genitalia, resembles a stricture. Before surgical treatment of vestibulovaginal stenosis (annular strictures) is considered for an intact animal, it should be evaluated during proestrus and estrus, at which time the normal vestibulovaginal junction relaxes considerably and is easily differentiated from a true stricture. Some strictures in the vestibule-vulva also "relax" during estrus. Abdominal radiography or ultrasonography can be performed to identify vaginal diverticula.

## **Treatment**

Anomalies of the vulva and vagina often are incidental findings. Treatment is unnecessary if they are causing no clinical signs. Anomalies of the vulva and vagina that are causing clinical signs should be corrected surgically, during anestrus. Vulvar anomalies are corrected by episioplasty. The prognosis after episioplasty for recovery from perivulvar dermatitis, recurrent urinary tract infection, and vaginitis is excellent. Episioplasty should be delayed until puppies have reached physical maturity and, whenever possible, obese animals have returned to normal body condition. Thin bands of persistent hymenal tissue can sometimes be broken using digital pressure alone. Some annular strictures are amenable to bougienage. Surgical repair is necessary for the treatment of vaginal septa, and this can be achieved with minimally invasive endoscopy or an episiotomy (see Fig. 57-3). The prognosis for normal mating ability after surgical correction of vaginal septa and hymenal remnants is excellent. Animals with annular strictures may be prone to fibrosis and restricture. Celiotomy may be necessary to correct a vaginal diverticulum. Because hypoplasia or agenesis cannot be rectified, affected animals should be neutered to prevent additional complications, such as cystic endometrial hyperplasia. The role that heredity plays in the development of congenital vaginal and vulvar anomalies in bitches is unknown, but it is known that certain vaginal anomalies are inherited in mice.

# CLITORAL HYPERTROPHY

In the female the clitoris develops from the genital tubercle, as does the penis in the male. Under the influence of androgens the canine clitoris may enlarge and even ossify. This can be caused by in utero exposure of female fetuses to androgens and progestins, by exogenous androgen administration to females of any age, or by endogenous androgen production from testicular tissue in intersex animals. Intersex is a term used to describe individuals with ambiguous genitalia in which the specific cause has not yet been determined. The cause may be abnormalities in chromosomal sex (e.g., XXY, XO, or XX/XY), gonadal sex (e.g., testis, ovotestis, and XX sex reversal), or phenotypic sex (e.g., ambiguous genitalia or discrepancy between internal and external genitalia, ±cryptorchidism). In utero exposure of female fetuses to androgens causes abnormal phenotypic sex. The external genitalia are ambiguous or cryptorchid male, whereas chromosomal sex is normal XX, the gonadal sex is normal ovary, and the internal genitalia are normal uterus, ±epididymis.

Clitoral hypertrophy may go unnoticed. More commonly, however, the enlarged clitoris protrudes from the vulva. This is often first apparent when the animal nears puberty or following the administration of exogenous androgens. A mucoid discharge is common, as is licking of the area. There may be a history of recurrent urinary tract infection. Physical examination will demonstrate the abnormal clitoris, which occasionally will have a distinctly phallic shape. When present, ossification is usually palpable. The vulva may have a normal appearance and position, or in intersex animals it may be ventrally displaced anywhere along the line from the normal vulvar position to the normal position of the preputial orifice (Fig. 57-4). This is because of the embryologic influence of androgens on the genital swellings, which normally develop into either the vulva (no androgen) or the prepuce and scrotum (androgen). The vestibule-vagina may be imperforate in females exposed in utero and in intersex animals.

Treatment is to remove the source of androgen if it still exists. The hypertrophic soft tissue of the clitoris will usually regress, but ossified tissue is usually permanent. Unless it is clear that a previously normal female has been treated with androgens, such as might be the case with racing Greyhound bitches, affected animals should be evaluated for the presence of an intersex condition. Exploratory laparotomy with the intent of removing the gonads and internal genitalia may be the most cost-effective approach, although hormonal testing to confirm the presence of testicular tissue and karyotyping easily can be done (see Chapter 56). Clitorectomy may be needed to eliminate the clinical signs associated with chronic exposure.

#### **VAGINITIS**

Vaginitis (i.e., inflammation of the vagina) occurs in sexually intact or neutered bitches of any age or breed during any

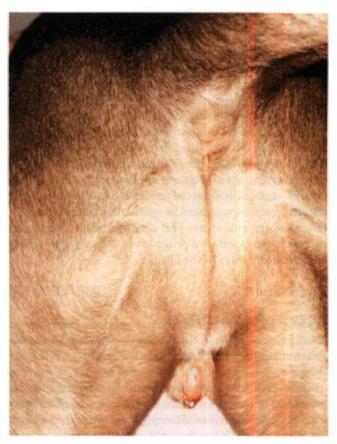


FIG 57-4
Clitoral hyperplasia in a 1-year-old Weimaraner examined because of recurrent urinary tract infection and vulvar discharge. Note the ventral displacement of the vulva. Testes and uterus were found at surgery. Gonadectomy, hysterectomy, and clitorectomy were curative.

stage of the reproductive cycle. It is rare in queens. Vaginitis may result from immaturity of the reproductive tract; anatomic abnormalities of the vagina or vestibule; chemical irritation, such as that caused by urine; bacterial, viral, or yeast infections; androgenic stimulation; or mechanical irritation, such as that caused by foreign material or neoplasia.

#### Diagnosis

The diagnosis is based primarily on the historical and physical finding of a mucoid, mucopurulent, or purulent vulvar discharge, which is present in most bitches (90%) with vaginitis. The vulvar discharge of vaginitis rarely contains blood, except in cases caused by foreign material or neoplasia. Licking of the vulva and pollakiuria are less common additional clinical signs that are present in about 10% of affected animals. Animals with vaginitis are otherwise normal and healthy. If they are not, a diagnosis in addition to, or other than, vaginitis should be pursued. For example, the vulvar discharge may be originating from the uterus, not the vagina, in the case of pyometra. The diagnosis of vaginitis can be substantiated by vaginal cytology and vaginoscopy, but this is not always necessary for a first occurrence. The cytologic

finding with vaginitis is nonseptic or septic inflammation without hemorrhage. Vaginoscopy is especially useful for identifying the underlying cause of vaginitis, such as anatomic abnormalities, foreign material, or neoplasia. The extent of the vaginal inflammation can also be assessed by vaginoscopy, and biopsies can be obtained if indicated. Urinalysis and urine culture should be performed in animals with a history of pollakiuria. Because the bacterial organisms isolated from bitches with vaginitis are quantitatively and qualitatively similar to the normal bacterial florae of the canine vagina, vaginal cultures are not helpful in the diagnosis of vaginitis. Rather, the results of bacterial culture and sensitivity testing are used to guide the formulation of a rational therapeutic plan. The clinical findings, diagnostic approach, treatment, and prognosis of canine vaginitis vary according to the age of the bitch.

#### **Treatment**

#### PREPUBERTAL BITCH

In bitches younger than 1 year of age, physical and historical abnormalities almost always consist only of the vulvar discharge and inflammation of the vulva and vagina. The animals are otherwise healthy. Vaginal cytologic findings are most often nonseptic in nature. Systemic or topical antibiotics, douches, and perineal cleansing are common treatments, but the evidence shows that 90% of young bitches recover from vaginitis with or without treatment. Therefore healthy young bitches in which clinical findings are limited to a nonhemorrhagic vulvar discharge usually need no further diagnostic tests and require no treatment. Most such animals recover spontaneously as they reach physical maturity. Whenever any additional historical or physical abnormali-

ties are found, young bitches should be evaluated using the approach described for the mature bitch.

The role of estrus, if any, in the resolution of vaginitis in young bitches is unclear. Because attaining physical and sexual maturity is so closely related, it is difficult to evaluate the relative contributions of each. In some bitches there is a temporal relationship between the onset of estrous activity and the resolution of vaginitis. However, vaginitis resolves spontaneously in most young bitches as they reach physical maturity, irrespective of estrus. Because ovariohysterectomy is traditionally performed before the first heat, the evidence is clear that ovariohysterectomy does not hasten the resolution of vaginitis. However, the effect of ovariohysterectomy on the persistence of vaginitis in the prepubertal bitch has not been reported. Because maturation of the reproductive tract during estrus may cause vaginitis to resolve (or, conversely, the absence of estrus may enable chronic vaginitis to persist), consideration may be given to delaying ovariohysterectomy in young bitches with chronic vaginitis until after the first heat.

# MATURE BITCH

A predisposing factor for vaginitis can be identified in most (70%) affected bitches older than 1 year. The key to the successful therapy of vaginitis in mature bitches is the identification and elimination of underlying disorders. Of the identifiable factors in mature bitches, abnormalities of the genital tract are the most common (35%). They are found during physical and endoscopic examinations and include vulvar anomalies, vaginal strictures, vertical vaginal septa, foreign material, clitoral hypertrophy, and vaginal neoplasia (Fig. 57-5). Disorders of the urinary tract, including urinary tract infection and urinary incontinence, are the next most



Vaginal abnormalities. A, Vaginal dermoid causing discharge in a 3-month-old Boxer.

B, Fibroma in an 11-year-old spayed Golden Retriever with swollen vulva, chronic mucopurulent discharge, and ovarian remnants with follicular cysts and luteoma.

commonly (26%) identified abnormalities in mature bitches with vaginitis. Therefore thorough physical examination and vaginoscopy to identify abnormalities in the genital tract, vaginal cytology to characterize the discharge, and analysis and culture of urine obtained by cystocentesis should always be included in the evaluation of mature animals with vaginitis. Canine herpes virus infection has been cited as a rare cause of vesicular lesions on the mucosal surfaces of the genitalia in bitches and dogs. The lesions are discovered on the vulvar mucosa or during vaginoscopy. They rarely cause discharge or other signs of vaginitis, and isolation of the virus is rarely reported. Much more commonly, canine herpes virus infection causes fulminant multiorgan system failure and death in neonates, mild respiratory infection in adults, and abortion.

The resolution of vaginitis in mature bitches is directly related to the elimination of the underlying disorder. The prognosis is excellent for resolution of vaginitis after vulvar and vaginal anomalies are surgically corrected, after foreign material is removed, and after urinary incontinence is controlled. Urinary tract infection and vaginitis have some mutual predisposing causes as well as being predisposing factors for each other. Fortunately, correction of mutual causes and appropriate antibiotic therapy usually resolve both, irrespective of which came first. The choice of antibiotics should be based on the results of urine culture. Some mature bitches with vaginitis recover spontaneously.

The role of estrus, if any, in resolving vaginitis in mature bitches is unknown. The signs of vaginitis continue to improve in some mature bitches with each succeeding cycle. In others there is no apparent change in response to estrus. The effects of ovariohysterectomy on vaginitis in mature bitches are even less clear. In most bitches ovariohysterectomy has no apparent therapeutic effect on the outcome. Signs of vaginitis occur after ovariohysterectomy in some previously healthy bitches.

# CHRONIC, NONRESPONSIVE VAGINITIS

Animals with chronic vaginitis in which an underlying cause has not been found and that do not recover in response to appropriate therapy remain a source of frustration. The initial minimum database of history, physical examination, urinalysis and urine culture, vaginal cytology, and vaginoscopy should be repeated. The database should be expanded to evaluate overall health with a complete blood count (CBC) and biochemical panel and to assess the rest of the urogenital tract with abdominal radiographs and ultrasound. The purpose is to assess progression of disease with the minimum database and find clues to less common predisposing factors or underlying disease with the additional diagnostic tests. For example, uterine stump abscess or pyometra or abnormal hormone production from ovarian remnant should be considered in the spayed bitch with chronic vaginitis. Yeast vaginitis, which is very uncommon in bitches, can occur after long-term antibiotic therapy. Body condition may have changed such that recessed vulva is now a factor. As a final diagnostic step, biopsy should be considered.

Some veterinarians recommend the use of over-the-counter douches containing dilute vinegar or povidone-iodine for the treatment of canine vaginitis. There is no published evidence that vaginal douching is efficacious in the treatment of canine vaginitis. In women douching is one of the risk factors for the development of bacterial vaginosis (Eckert, 2006). Povidone-iodine is cited as a contact irritant cause of noninfectious vaginitis and vulvitis in women (Sobel, 1997). Given the anatomy of the canine vagina, the discomfort of vaginitis, and the need for adequate animal restraint, many pet owners are unable to instill douches into the vagina instead of the vestibule. Until there is evidence that douching is helpful and that it is not harmful in management of canine vaginitis, the practice should probably be discontinued.

# **NEOPLASIA**

Leiomyoma is the most common neoplasm of the vagina and uterus in geriatric bitches and queens. It often causes hemorrhage. However, because leiomyomas do not exfoliate readily, neoplastic cells are usually not seen on cytologic preparations. The histologic diagnosis is made from biopsy specimens of the mass that is identified by palpation, diagnostic imaging, and/or vaginoscopy. Treatment of leiomyomas is surgical excision. The prognosis is good if the location of the tumor is amenable to complete surgical excision. Transitional cell carcinoma (TCC) occasionally invades the vestibule-vagina from the urethra. When it does, it can often be detected by vaginal palpation and can be seen during vaginoscopy. TCCs readily exfoliate, and the diagnosis is easily made on the basis of cytology obtained directly from the lesions during vaginoscopy (see Fig 57-1). Treatment of TCC is chemotherapy. The prognosis for cure is guarded, but quality of life may be good while urine flow is maintained and urinary tract infection and inflammation are controlled.

Bitches with transmissible venereal tumors (TVTs) are more likely to be examined because of a mass protruding from the vulva than because of a vulvar discharge. TVT is a contagious round-cell tumor. Venereal transmission is most common. It occurs primarily on the mucosal surfaces of the external genitalia of male and female dogs, but it can be transplanted to other sites and transmitted to other dogs by licking and by direct contact with the tumor. Primary TVTs have been found on the skin and in the oral and anal mucous membranes. The prevalence of TVT varies greatly with the geographic area. For example, the prevalence of TVT among 300 pound-source bitches in Yucatan, Mexico, was 15% (Ortega-Pacheco et al., 2007). Some TVTs regress spontaneously, but most do not. Some TVTs are quite locally invasive, and some metastasize to the regional lymph nodes (Fig. 57-6). Rarely, metastasis to distant sites such as the lungs, abdominal viscera, or central nervous system (CNS) occurs.

TVTs have a fleshy, hyperemic appearance. Initially, they appear as a raised area. As they grow, they acquire a



FIG 57-6 Invasive transmissible venereal tumor of the vulva.

cauliflower-like shape and may reach a diameter of 5 cm or larger. They are often quite friable and bleed easily. TVTs in males are most often found on the bulbus glandis area of the penis, but they may appear anywhere on the penile or preputial mucosa. Affected animals are usually examined because of a mass on the external genitalia, but they may also be seen because of a preputial or vulvar discharge. The diagnosis of TVT is strongly suspected on the basis of the physical appearance of the tumor on the external genitalia. Differential diagnoses, especially in animals with nongenital lesions, include other round-cell tumors such as mast cell tumor, histiocytoma, and lymphoma. Pyogranulomatous lesions and warts of the genitalia may also have a similar gross appearance. The diagnosis of genital TVT is easily confirmed by exfoliative cytologic studies, fine-needle aspiration, or histopathologic findings.

TVTs respond to several chemotherapeutic agents. Vincristine, administered once weekly as a single agent (see Chapter 77), is quite effective for solitary, localized lesions. It has a low toxicity and is financially acceptable to most owners. It is administered for two treatments beyond the time when the tumor disappears. The total duration of treatment is usually 4 to 6 weeks. Complete remission is achieved in more than 90% of dogs treated with vincristine alone, and they usually remain disease free. TVTs are also extremely sensitive to radiation therapy. Although surgical excision results in long-term control, relapses occur in as many as 50% of animals.

# VAGINAL HYPERPLASIA/PROLAPSE

During proestrus and estrus the vagina becomes edematous and hyperplastic. Sometimes, the change is so severe in bitches that vaginal tissue protrudes out of the vulva. This condition has been referred to as *vaginal hyperplasia* or *vaginal prolapse* because these are the most prominent microscopic and physical findings, respectively. Vaginal hyperplasia/prolapse occurs in bitches exclusively during

times of estrogenic stimulation—in other words, during proestrus and estrus. On rare occasions, prolapse recurs later in the same cycle at the end of diestrus or at parturition, a time when additional estrogen may be secreted. It is common for vaginal hyperplasia/prolapse to recur during each estrus in affected individuals, although each episode is not always of the same severity.

The amount of edema and hyperplasia is extremely variable. Digital palpation of the vagina shows that the mass originates from the ventral vagina, immediately cranial to the urethral orifice. All other areas of the vagina are normal. If the edematous tissue is small enough to be contained within the vagina and vestibule, it is usually very smooth, glistening, and pale pink to opalescent because of the edema (type I vaginal prolapse; Fig. 57-7, A). If the hyperplastic tissue protrudes from the vulva, it is dry, dull, and wrinkled. With continued exposure, fissures and ulcers develop (type II vaginal prolapse; Fig. 57-7, B). Although the tissue protruding from the vulva may be quite massive, it originates from a stalk involving only a few centimeters of the vaginal floor. Much less commonly, the hyperplastic tissue involves the circumference of the vagina (type III; Fig. 57-7, C). In all three types of vaginal hyperplasia/prolapse, the tissue is located at the level of the urethral orifice; the rest of the vagina is normal. Despite the fact that the edematous hyperplastic tissue lies over the external urethral orifice, urine flow is rarely impeded.

The diagnosis of vaginal prolapse is made on the basis of the history and physical examination findings. Bitches may be seen because they refuse to allow intromission or because of the mass protruding from the vulva. The history indicates that they are in proestrus or estrus. If it does not, the stage of the cycle can be confirmed by vaginal cytology. The protrusion of this edematous, hyperplastic tissue must not be confused with a true prolapse of the vagina or uterus that occurs rarely during parturition (Fig. 57-8). The history alone (estrus versus parturition) should be sufficient to do so. If the clinician is concerned that the hyperplastic tissue could be neoplastic, the two can be differentiated on the basis of findings yielded by the cytologic examination of material obtained by fine-needle aspiration.

#### **Treatment**

The treatment of vaginal hyperplasia/prolapse is primarily supportive. The edema and hyperplasia will resolve spontaneously when the follicular phase of the cycle and the ovarian production of estrogen are over. This can be hastened by ovariohysterectomy. Ovariohysterectomy also prevents the recurrence of vaginal hyperplasia/prolapse because there will be no more estrous cycles. After oophorectomy the edema and hyperplasia usually resolve within 5 to 7 days. There is no published evidence that the pharmacologic induction of ovulation hastens recovery.

Exposed tissue must be protected from trauma and, if the mucosa is damaged, from infection. This is usually accomplished by applying topical antibiotic (e.g., bacitracinneomycin-polymyxin) or antibiotic-steroid creams and







Vaginal hyperplasia and prolapse. A, Type I, edema.

B, Type II. C, Type III.

cleaning the tissue (with warm saline solution or warm water and pHisoHex) as needed. Attention should also be paid to the underlying perineal and vulvar skin, which may be subject to maceration (see Fig. 57-7C). Potentially irritating bedding such as straw or wood chips should be removed. An



FIG 57-8
Periparturient vaginal prolapse in a cat.

Elizabethan collar may be used to prevent self-mutilation, but this is rarely necessary. Artificial insemination can be performed if vaginal hyperplasia/prolapse prevents copulation. The condition will resolve spontaneously as soon as the female goes out of heat. It is unlikely to recur (although this is possible) and cause dystocia at the time of parturition.

Surgical resection of the edematous tissue has been considered for brood bitches, but this should probably be reserved for extremely valuable animals. The hemorrhage that results is often significant, despite excellent surgical technique. The resection of hyperplastic tissue also does not prevent recurrence during subsequent estrous cycles, although the severity of the prolapse may be markedly reduced. We have seen one bitch with recurrent hyperplasia/ prolapse in which the prolapse did not resolve despite ovariohysterectomy after the fourth recurrence. Resection was the only recourse. Because of its recurrent nature and the care required to manage severe cases, affected animals are not the best brood bitches. The role that heredity plays, if any, in the development of vaginal hyperplasia/prolapse is not known, but it appears to be at least familial in nature.

# **DISORDERS OF THE UTERUS**

The clinical signs of disorders of the uterus are variable and nonspecific. For example, there may be no clinical signs associated with congenital anomalies such as segmental aplasia. Rather, it may be an incidental finding at the time of elective ovariohysterectomy. Conversely, in cycling animals segmental aplasia may be the cause of infertility. Many uterine disorders are manifested by the presence of an abnormal vulvar discharge. Uterine enlargement may cause abdominal discomfort and abdominal distention. In addition to those signs, uterine infections typically cause signs of systemic illness, such as anorexia, lethargy, polydipsia-polyuria, or fever. Uterine disease should be considered among the ruleouts for infertility, vulvar discharge, and postpartum illness. Uterine disease is much more likely in sexually intact animals,

but the history of having been spayed does not exclude the possibility of a uterine stump abscess or granuloma, or pyometra in an animal with ovarian and uterine remnants.

Determining the stage of the estrus cycle is important for several reasons. First, some disorders are seen during certain stages; for example, pyometra is almost always seen during diestrus. Second, interpretation of diagnostic tests, such as cytology of vulvar discharge, depends on knowledge of the cycle. Physical examination will assess the overall health, and identify abnormalities in the reproductive tract. Uterine enlargement is usually detectable by abdominal palpation, especially in cats. Vulvar discharge may be more evident after palpation of the uterus. The absence of these findings, however, does not exclude uterine disease. Diagnostic imaging, particularly abdominal ultrasound, is extremely helpful. A uterine source of a vulvar discharge can be confirmed by vaginoscopy. Whenever there are signs of systemic illness, a CBC, biochemical panel, and urinalysis are indicated. The most common uterine disorders causing systemic illness in dogs and cats are pyometra (discussed later) and postpartum metritis (see Chapter 59).

Uterine neoplasia is rare in dogs and cats. Leiomyoma is the most common. Rarely, adenocarcinoma has been reported. Uterine neoplasia may be an incidental finding, or it may be associated with sangineous vulvar discharge, anorexia, weight loss, and abdominal discomfort and enlargement. The diagnosis is made by the finding of uterine enlargement on abdominal palpation and diagnostic imaging. Treatment is ovariohysterectomy. The prognosis for uterine leiomyoma is good if the location of the tumor is amenable to complete surgical excision. The prognosis for uterine carcinoma is poor because metastasis is often present. Focal, benign uterine masses, such as adenomomas, have also rarely been reported in geriatric bitches.

Uterine torsion is a life-threatening condition that usually occurs in the near-term gravid uterus in bitches and queens. It has also been reported in conjunction with other uterine pathology, such as hematometra and pyometra. One or both horns may be involved (Fig. 57-9). Affected animals are usually very ill and present as an acute abdomen with abdominal splinting and pain. Clinical signs also include sanguineous vulvar discharge and straining. The diagnosis is suspected on the basis of physical examination and ultrasonographic findings. It is confirmed at surgery. There are often significant metabolic derangements that should be evaluated with a biochemical panel and/or venous blood gas analysis. Treatment is ovariohysterectomy and intensive supportive therapy.

# CYSTIC ENDOMETRIAL HYPERPLASIA, MUCOMETRA, AND PYOMETRA

# CYSTIC ENDOMETRIAL HYPERPLASIA

Cystic endometrial hyperplasia (CEH) is characterized by an increase in the number, size, and secretory activity of the endometrial glands and by endometrial hyperplasia. Proges-



FIG 57-9
Torsion of both uterine horns.

terone plays the most prominent role in the development of CEH, although it is not the only mechanism by which CEH can be experimentally induced. In bitches and queens CEH develops during the luteal phase (diestrus) of the cycle, a time when endogenous progesterone concentrations are high. It also develops in response to exogenous progestins under therapeutic as well as experimental conditions. The most common therapeutic use of progestins in bitches and queens is to suppress estrus. The endometrial response to endogenous and exogenous progesterone seems to be dose dependent because most affected animals are middle-aged, having experienced multiple cycles or having been treated for a length of time. In experimental conditions, as well as clinical application, the addition of estrogen when serum progesterone concentrations are high, such as is the case when estrogens are used for "mismating" in bitches, enhances the development of CEH, whereas estrogen alone does not cause CEH. Under experimental conditions ovariectomized 2- to 4-year-old bitches given a progestin (megestrol acetate) for 30 days developed CEH that was reversible when the progestin was withdrawn but that persisted when the progestin was continued. The same experiment confirmed previous findings that mechanical irritation of the endometrium (in this case by implanting silk suture material) also can cause CEH, but the silk-induced CEH was not maintained in the absence of the progestin (Chen et al., 2006). In and of itself, CEH does not cause clinical illness. Cystic endometrial hyperplasia does cause increased thickness in the uterine wall, which may be detectable on abdominal palpation and ultrasound. It may also cause decreased fertility.

## **MUCOMETRA**

The general consensus is that CEH is the precursor of mucometra or hydrometra. In addition to the fluid accumulation within the cystic endometrial glands, sterile fluid accumulates in the uterine lumen. There may also be a mucoid or seromucoid vulvar discharge if the cervix is open. The dis-



**FIG 57-10 A,** Cat mucometra. **B,** Canine pyometra with severe cystic hyperplasia.

charge is not purulent on cytologic evaluation. Uterine enlargement is detected by abdominal palpation and with diagnostic imaging. The uterus can be large enough to cause abdominal distention and associated signs of discomfort. Because bitches normally experience diestrus lasting more than 60 days after every estrous cycle and because queens usually experience diestrus only after having been induced to ovulate, mucometra is much more common in bitches than in queens.

Some bitches with mucometra also have a history of polydipsia-polyuria and vomiting or anorexia, but vital signs usually are normal and attitude usually is good. Ultrasonography will demonstrate the luminal fluid as well as the character of the uterine wall. Usually, the wall will be thicker than normal and the cystic nature of the endometrium is evident (Fig. 57-10). However, in some cases the histopathologic finding is endometrial atrophy. This may be related to the duration and degree of uterine distention. The historical and physical findings of animals with mucometra can be very similar to those of pregnancy or pyometra. Pregnancy can easily be excluded on the basis of ultrasound, but before days 42 through 45 of gestation when fetal skeletons become visible, the radiographic appearance of mucometra and the pregnant uterus is the same. Differentiating animals with mucometra from those with pyometra may be more difficult. Ultrasound alone would not be sufficient to differentiate among hydrometra, mucometra, and pyometra, but hydrometra and mucometra typically have a relatively anechoic ultrasonographic appearance, whereas the fluid associated with pyometra is usually echogenic. Animals with mucometra are not seriously ill, whereas those with pyometra often are. Both groups of animals are likely to be mildly anemic. The mean total WBC count of bitches with mucometra is normal, although an individual animal may have counts as high as 20,000/µl; whereas the mean total WBC of bitches with pyometra is reported to about 23,000/µl, with great variation among individuals. The most striking difference on the hemogram is the percentage of band neutrophils, which are much higher in bitches with pyometra. Fransson et al. (2004) reported that the percentage of band neutrophils had

a sensitivity of 94% in differentiating pyometra from mucometra. Animals with mucometra typically have normal biochemical results. Ovariohysterectomy is curative. Medical management, as for pyometra, could also be considered for valuable breeding animals with mucometra.

#### **PYOMETRA**

Pyometra is characterized by purulent uterine contents and histologic evidence of variable degrees of inflammatory cell infiltrates (neutrophils, lymphocytes, plasma cells, macrophages) in the endometrium and, in severe cases, in the myometrium. There is also cystic endometrial hyperplasia, which is sometimes severe. Mild to severe fibroblast proliferation in the endometrial stroma, variable degrees of edema, necrosis, and sometimes ulceration of the endometrium and abscess formation in the glands are found. Occasionally, there is severe inflammation in the endometrium and myometrium, with endometrial atrophy rather than hyperplasia (De Bosschere et al., 2002). What initiates pyometra is still not completely understood. Although progesterone clearly plays a role, it is apparently not the sole explanation because serum progesterone concentrations are similar among normal healthy bitches and bitches with CEH, mucometra, and pyometra. It is also evident that neither CEH nor mucometra invariably progresses to pyometra. Differences in uterine estrogen and progesterone receptors have been demonstrated among normal, CEH, and pyometra specimens, but the differences have not always reached statistical significance and have not clearly demonstrated a different pathogenesis.

Bacterial invasion, presumably from the vaginal florae, is an important trigger. *Escherichia coli* is the most common organism isolated from bitches and queens with pyometra. Gram-negative bacteria such as *E. coli* produce endotoxins that are capable of initiating the cytokine cascade and the release of many inflammatory mediators. These are thought to be the cause of the local and systemic inflammatory reactions associated with pyometra. Inflammatory mediators such as C-reactive protein, tumor necrosis factor—1, lactoferrin, and PGF<sub>2 $\alpha$ </sub> are present in significantly greater serum or

uterine concentrations in bitches with pyometra than in normal animals. Serum concentrations of C-reactive protein and PGF<sub>2 $\alpha$ </sub> are significantly greater in bitches with pyometra than in bitches with CEH alone. In addition to the local and systemic inflammatory response, bitches with pyometra are immunosuppressed as assessed by lymphocyte blastogenesis.

As with mucometra, pyometra is more common in bitches than in queens. Age, previous hormonal therapy, and nulliparous status are risk factors for the development of pyometra. The risk of developing pyometra increases with age, presumably because of repeated hormonal stimulation of the uterus. Reported mean ages of bitches with pyometra range from 6.5 to 8.5 years. There is a sixfold increased risk of pyometra in nulliparous bitches compared with primiparous or multiparous animals. Previous hormonal therapy with progestins and estrogen is also a risk factor. Estrogens given during diestrus, a time when endogenous serum concentrations of progesterone are high, increase the risk of pyometra. Younger bitches (mean age 5.5 years) that develop pyometra were more likely than older bitches (mean age 8.5 years) to have been treated with estrogens (Niskanen et al., 1998). Analysis of survival rates in Swedish dogs indicates that, on average, about 24% of bitches will develop pyometra by age 10 years. In Sweden progestins, rather than ovariohysterectomy, are the most common method used to control estrus.

#### **Clinical Features**

Pyometra is a serious, potentially life-threatening disorder because septicemia and endotoxemia can develop very quickly (over a matter of hours) and at any time. For this reason it is usually treated as an emergency situation. The clinical signs become evident during diestrus or early anestrus. The history typically shows that the female was in heat 4 to 8 weeks earlier or that progesterone was recently given, either as a treatment or as contraception. Owners often report a vulvar discharge. The other historical findings are not specific for pyometra. They include lethargy, anorexia, and vomiting. Polydipsia-polyuria is a common finding in bitches but not in queens. On physical examination a purulent, often bloody vulvar discharge is found in most (85%) bitches and queens with pyometra. Pyometra is classified as open or closed depending on whether there is a vulvar discharge. The degree of uterine enlargement is variable. Dehydration is a common finding, as is abdominal discomfort. Other physical examination findings vary according to the severity of sepsis or endotoxemia. Most affected animals are lethargic. Rectal temperature is often normal. Fever is reported in only 20% to 30% of bitches and queens with pyometra. Subnormal temperature may be found in those in septic or endotoxic shock. Capillary refill time may be prolonged.

#### Diagnosis

The diagnosis of pyometra is strongly suspected on the basis of the occurrence of clinical signs in a sexually mature female

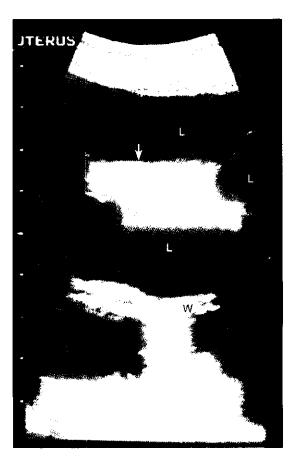


FIG 57-11 Sonogram of pyometra. L, Fluid-filled uterine lumen; W, uterine wall; arrow, endometrial cysts.

during or shortly after diestrus or after exogenous progestin administration, the presence of a septic vulvar discharge, and uterine enlargement. Abdominal ultrasound (or radiographs taken more than 45 days after having been in heat) confirms a fluid-filled uterus and rules out pregnancy (Fig. 57-11; see also Fig. 56-9). Neutrophilia with a shift toward immaturity (band neutrophils), monocytosis, and evidence of WBC toxicity are the most common findings on the CBC. The left shift (band neutrophils) is the single most sensitive test to differentiate pyometra from mucometra. Animals with pyometra may have a total WBC count as high as 100,000 to 200,000/µl, or there may be a leukopenia with a degenerative left shift. A mild normocytic, normochromic, nonregenerative anemia is usually also evident. Biochemical abnormalities are common, but nonspecific for pyometra. They include hyperproteinemia, hyperglobulinemia, and azotemia. Occasionally, alanine aminotransferase and alkaline phosphatase activities are mildly to moderately increased. Urinalysis findings include isosthenuria and/or proteinuria in one third of the bitches with pyometra. Bacteriuria is common.

There is often a prerenal component to the azotemia. Most bitches and queens with pyometra are middle-aged or older and may have preexisting renal disease. Additionally, azotemia, proteinuria, and isosthenuria are often a direct result of the pyometra and are potentially reversible once the

uterine infection is resolved. Immune complex glomerulonephritis is thought to be the cause of pyometra-induced azotemia and proteinuria. Even without overt azotemia, it has been shown that most (75%) bitches have decreased glomerular filtration rates as determined by ioxhexol clearance. The decreased glomerular filtration rate is demonstrable irrespective of age, indicating that pyometra, not solely preexisting renal disease, is a factor. The complete pathophysiology of the isosthenuria and polyuria has not been elucidated. It has been demonstrated that the ability to secrete vasopressin is not diminished in these animals but that the renal tubules of bitches with pyometra do not respond adequately to vasopressin. It is thought that bacterial endotoxin interferes with renal tubular response. Vaginal cytology reveals a septic exudate, sometimes containing endometrial cells (see Fig. 57-1). Results of bacterial culture and sensitivity testing of the uterine exudate identify the offending organism and the appropriate antibiotic therapy.

The most important alternate diagnosis for pyometra is pregnancy. Both conditions occur during the diestrous stage of the cycle. A modest mature neutrophilia, mild anemia, and hyperglobulinemia normally occur during pregnancy. Pregnant animals are not always healthy, and the presence of a septic vulvar discharge does not preclude the possibility of co-existent pregnancy. Uterine infection during pregnancy does not invariably result in the death of all fetuses. Even in the event of overt abortion, the entire litter is not always lost. The owner's goals of treating an ill pregnant animal may be quite different from the goals of treating one with pyometra.

#### **Treatment**

Treatment of pyometra must be prompt and aggressive if the animal's life is to be saved. Septicemia, endotoxemia, or both can develop at any time if they do not already exist. Uterine rupture also sometimes occurs. Intravenous fluid therapy is indicated to correct existing deficits, maintain adequate tissue perfusion, and improve renal function. Very aggressive fluid therapy will be needed for animals in septic shock. Even if they survive ovariohysterectomy, postoperative mortality is higher in bitches when blood pressure and urine output remain low than among those in which fluid therapy corrected hypotension and increased urine output. Whether or not they are septic, the prognosis for survival is worse when azotemia cannot be resolved before ovariohysterectomy. Appropriate antibiotic therapy should be instituted as soon as possible. Pending the culture results, an antibiotic that is typically effective against E. coli, the organism most commonly isolated from pyometra, could be considered. These include enrofloxacin, trimethoprim-sulfa, and amoxicillinclavulanate. Ovariohysterectomy is the treatment of choice for pyometra in bitches and queens. Despite appropriate supportive and surgical treatment, morbidity of 3% to 20% and mortality of 5% to 28% are reported. This is not unexpected, given the serious metabolic derangements caused by pyometra. Barring complications resulting from the disease itself, surgery, or anesthesia, ovariohysterectomy is curative.

# **Nonsurgical Treatment of Pyometra**

Whether surgical or nonsurgical treatment is chosen, the needs for fluid and antibiotic support must be addressed. The justifications for the medical, rather than surgical, treatment of pyometra are the owner's desire for offspring from the affected female and the health of the animal. Although medical management may effectively resolve the clinical illness and preserve the potential for future litters, unlike ovariohysterectomy, medical management of pyometra is not curative. Pyometra can be expected to recur. Recurrence is more common in bitches than in queens because bitches will have progesterone stimulation, the factor initiating pyometra, for at least 60 days after every cycle. Queens, on the other hand, are under the influence of progesterone only after copulation-induced ovulation or, less commonly, after spontaneous ovulation. Recurrence rates of 20% to 25% after the next estrus, 19% to 40% by 24 months, and 77% by 27 months after nonsurgical treatment of pyometra are reported for bitches. Recurrence rates of 7% to 15% are reported for queens. Some of the animals in these reports successfully became pregnant before pyometra recurred, whereas others did not. Because reproductive performance is limited by recurrence, the desired number of offspring should be obtained as soon as possible. Breeding to a fertile male during the first posttreatment estrus is recommended. Although there are reports of successful medical treatment of recurrent pyometra in bitches and queens, ovariohysterectomy, rather than repeated attempts at medical management, is usually recommended.

The other important consideration for medical, as opposed to surgical, treatment of pyometra is the animal's health. Medical treatments take days to weeks to rid the animal of the infected uterine contents, whereas ovariohysterectomy accomplishes this in a matter of hours. Surgery is the better choice for critically ill animals. Response to medical treatment is much better in animals with open-cervix pyometra than in those with a closed cervix. Unless the cervix dilates during treatment of closed-cervix pyometra, treatment will fail. There is a greater risk of uterine rupture. For these reasons ovariohysterectomy should be considered for animals with closed-cervix pyometra even if they are not critically ill.

A variety of luteolytic and uterotonic drugs are used to treat pyometra. Luteolysis is important to stop continued progesterone production. Myometrial contractions are necessary to expel the uterine contents. Dopamine agonists such as bromocriptine and cabergoline suppress luteal activity by suppressing prolactin, which is luteotropic in bitches. Prostaglandins, such as prostaglandin  $F_{2\alpha}$  and cloprostenol, cause luteolysis via apoptosis, and they also cause myometrial contractions. Competitive antagonists of the progesterone receptor, such as aglepristone, block the effects of progesterone, and this results in cervical dilation and uterine contractions. Women who might be pregnant should handle all these drugs with great care. These drugs have been used alone and in combination with each other according to a variety of protocols that have been designed to minimize side

# Nonsurgical Treatment of Pyometra

All treatments are "to effect," as described in the text:

- Resolution of clinical signs
- 2. Empty uterine lumen
- 3. Return toward normal uterine wall

Note: Several drug dosages are given in micrograms, µg

#### Prostaglandin $F_{2\alpha}$ as a Single Agent

Prostaglandin  $F_{2\alpha}$ , 0.1-0.25 mg/kg, SC, q24h or q12h (Lutalyse<sup>®</sup>, Pfizer, New York City)

#### Cabergoline and Cloprostenol

Cabergoline, 5 µg/kg, PO, q24h for 7 days (Dostinex®, Pfizer, New York City, can be compounded to the appropriate concentration) (Galastop®, Ceva Vetem, Milan, Italy)

Cloprostenol, 1 µg/kg, SC, q24h for 7 days; if no response, continue cloprostenol alone, without cabergoline, for 7 more days [Estrumate®, Schering-Plough, Union, NJ)

#### Aglepristone and Cloprostenol

Aglepristone, 10 mg/kg, SC, once daily on days 1, 2, and 8 (Alizine®, Virbac, Carros, France)

Cloprostenol, 1 µg/kg, SC, once daily on days 3-7 (Estrumate®, Schering-Plough, Union, NJ)

Reevaluate on day 14; if not resolved, administer one dose of aglepristone, 10 mg/kg, SC, on day 14

SC, Subcutaneous; PO, oral.

effects and take advantage of their different modes of action. Treatment is continued until the uterus is empty, which is typically 7 to 14 days. During treatment the vaginal discharge is expected to increase as the uterus empties, and the animal's clinical condition and laboratory abnormalities are expected to improve. If the clinical status worsens during medical treatment, ovariohysterectomy should be performed instead. Ovariohysterectomy can be considered at any time during medical treatment of pyometra if the condition is not improving as expected. Some of the treatment protocols are summarized in Box 57-2. These drugs are not labeled for use in dogs or cats in the United States at this time, although veterinary preparations are available in many other countries.

Adverse reactions are common in animals receiving  $PGF_{2\alpha}$  (Lutalyse®, Pfizer) therapy and include panting, salivation, emesis, defecation, urination, mydriasis, and nesting behavior. Intense grooming behavior and vocalization may also be seen in the queen. Adverse reactions usually develop within 5 minutes of  $PGF_{2\alpha}$  administration and last for 30 to 60 minutes. The severity of reactions is directly related to the dose administered and inversely related to the number of days of therapy. Adverse reactions tend to become milder with subsequent injections. Fewer side effects are reported for cloprostenol (Estrumate®, Schering-Plough), but gastro-

intestinal signs still occur in 30% to 54% of bitches given the drug. Gastrointestinal signs are the most common side effect of cabergoline (Galastop®, Ceva Vetem; Dostinex®, Pfizer). The only side effect reported for Aglepristone (Alizine®, Virbac) is transient pain or swelling at the injection site. Massaging the injection site to help disperse the drug can minimize this reaction. The posttreatment interestrous interval is shortened by 1 to 3 months by all of these drugs.

Pregnancy rates of 80% to 90% are reported for bitches that have received PGF<sub>2 $\alpha$ </sub> therapy for open-cervix pyometra, whereas pregnancy rates are only 25% to 34% in bitches with closed-cervix pyometra. Pregnancy rates of 70% to 90% are reported for queens after PGF<sub>2α</sub> treatment for open-cervix pyometra. The successful treatment with PGF<sub>2α</sub> of closedcervix pyometra in queens has apparently not yet been reported in the English-language literature. Other studies have focused more on survival of the animals than on subsequent fertility. In these studies success was defined as the resolution of clinical illness, absence of intraluminal uterine fluid, and return of uterine horn diameter to normal as assessed by ultrasound. Treatment with a combination of cloprostenol and cabergoline for 7 to 14 days was considered successful in 24 of 29 bitches (83%) with open-cervix pyometra when the bitches were evaluated at 14 days (Corrada et al., 2006). The other five bitches were spayed at 14 days. Only two of the successfully treated bitches were subsequently bred, and one conceived. Six of the bitches (25%) had a recurrence of pyometra after the first posttreatment estrus. Treatment with combinations of cloprostenol and aglepristone for 8 to 15 days was successful in 60% to 75% of bitches (n = 15) with open-cervix pyometra when the bitches were evaluated at 15 days, and all 15 bitches had returned to normal by 29 days (Gobello et al., 2003). Three of the 15 remaining bitches (20%) had a recurrence of pyometra after the first posttreatment estrous cycle. Only one bitch was mated, and she did conceive.

Fieni (2006)studied the efficacy of aglepristone given alone on days 1, 2, and 8 or in combination with cloprostenol on days 3 through 7 in 52 bitches with pyometra. Aglepristone caused the cervix to open within 4 to 48 hours (mean = 26 hours) in all 17 of the bitches with closed-cervix pyometra. The animals' clinical condition improved immediately thereafter. Treatment of pyometra with the combination of aglepristone and cloprostenol was more successful (84%) than was treatment with aglepristone alone (60%). Five bitches were mated during the first posttreatment estrus, and 4 (80%) became pregnant. Two bitches that did not respond to treatment died 5 and 15 days later. Of the successfully treated bitches, 13% had recurrence of pyometra by 12 months after treatment and 19% had recurrence by 24 months after treatment. Treatment was successful even when serum concentrations of progesterone were already below 1 ng/ml at the onset of treatment. This would support the concept that the pathogenesis of pyometra is related to the interactions of progesterone with progesterone receptor and not solely to high serum concentrations of progesterone. The absence of side effects and the rapidity with which aglepristone caused cervical dilation in bitches with close-cervix pyometra suggest that aglepristone may be beneficial in presurgical stabilization of bitches undergoing ovariohysterectomy for pyometra. This possibility deserves further study.

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# CHAPTER

# False Pregnancy, Disorders of Pregnancy and Parturition, and Mismating



# CHAPTER OUTLINE

FALSE PREGNANCY NORMAL EVENTS IN PREGNANCY AND PARTURITION

Fecundity

Pregnancy Diagnosis

Alterations in Bitch and Queen During Pregnancy

Gestation Length

Parturition

**Predicting Labor** 

Stages of Labor

**DYSTOCIA** 

PREGNANCY LOSS

Mycoplasma

Brucella canis

Herpes Virus

Other Causes of Pregnancy Loss

OTHER PREGNANCY DISORDERS MISMATING (ABORTIFACIENTS)

Estrogens

Prostaglandins

Alternative Treatments

# **FALSE PREGNANCY**

# Etiology

False pregnancy is a clinical phenomenon in which a female that was not pregnant displays maternal behavior such as nesting, the adoption of inanimate objects or other animals, mammary gland development, and lactation. False pregnancy occurs commonly in intact, cycling bitches and is considered to be normal. It occurs after diestrus (i.e., luteal phase), when serum concentrations of progesterone decline. The terms *false pregnancy*, *pseudopregnancy*, and *psuedocyesis* are often used interchangeably, but none accurately reflects the situation in bitches in which the clinical signs occur during what would have been the postpartum period, not during what would have been the pregnant period (i.e., luteal

phase) of the cycle. Progesterone causes mammary gland development and weight gain, irrespective of pregnancy status. The drop in serum concentrations of progesterone at the end of diestrus causes an abrupt increase in prolactin secretion, which causes lactation and the behavioral changes of false pregnancy. Because the bitch ovulates spontaneously and always enters a long luteal phase, false pregnancy is a common phenomenon in cycling bitches. It is uncommon in queens. In bitches false pregnancy also occurs after the withdrawal of exogenous progestins and after oophorectomy performed during diestrus.

False pregnancy is considered a normal phenomenon in bitches. It is not associated with any reproductive abnormalities, including cycle irregularities, pyometra, or infertility. To the contrary, the occurrence of false pregnancy provides evidence that ovulation took place during the preceding cycle and that the hypothalamic-pituitary-gonadal axis is intact. Why some bitches are prone to developing clinical signs and why the severity of the clinical signs vary from cycle to cycle are not known. Although serum concentrations of prolactin do increase when progesterone is withdrawn, they are not always elevated to the same degree, nor are they always found to remain elevated by the time bitches are evaluated for false pregnancy. This may be due in part to the 6-hour pulsatile secretion pattern of prolactin, which makes interpretation of the results of a single blood sample less reliable. Nevertheless, at similar prolactin concentrations some bitches show clinical signs of false pregnancy and others do not. Some individual predisposition toward the development of false pregnancy evidently exists. In addition, factors relating to nutrition influence the occurrence of false pregnancy. Thin bitches are less likely to experience false pregnancy than bitches of the same breed in ideal body condition.

# **Clinical Features**

The most common clinical signs of false pregnancy are mammary gland enlargement and lactation. The mammary secretion varies from a small amount of clear or brownish fluid to large amounts of milk that may drip spontaneously from the glands. Nesting behavior is the next most common clinical sign of false pregnancy. Many bitches will "adopt" things. Some animals also experience restlessness, irritability, abdominal enlargement, anorexia, and vomiting. The diagnosis is based on the historical and physical findings in a nonpregnant bitch or, less commonly in a queen, at the end of diestrus. It may also occur after oophorectomy during diestrus or when exogenous progestins are discontinued. Before treatment of false pregnancy is undertaken, it is essential that the evaluation, such as diagnostic imaging, be sufficient to rule out pregnancy because all treatments for false pregnancy will be deleterious to pregnancy, should it exist.

#### **Treatment**

False pregnancy is a normal, self-limiting phenomenon in bitches that usually does not require treatment. The clinical signs usually resolve after 2 or 3 weeks. Stimulation to the mammary glands, such as licking, can promote lactation. Withholding food for 24 hours, followed by a gradual (i.e., 3 to 5 days) increase back to usual quantities, helps to reduce lactation. When treatment is needed, drugs that inhibit prolactin release, such as dopamine agonists and serotonin antagonists, are effective in ameliorating the behavioral and physical signs of false pregnancy in bitches. These drugs are not labeled for veterinary use in the United States at this time. The dopamine antagonist cabergoline (Galastop®; Ceva Vetem; Dostinex®, Pfizer), 5 µg/kg orally, once daily, causes improvement in 3 to 4 days, with the signs resolving by 7 days. Dostinex® can be compounded to the appropriate concentration. Cabergoline may cause vomiting and, rarely, increased aggression. The serotonin antagonist metergoline (Contralac®; Virbac Laboratories) also inhibits prolactin secretion. The suggested dose is 0.1 to 0.2 mg/kg twice daily for 8 days. It does not cause vomiting but can cause hyperexcitability, aggression, and whining. Mild tranquilization can be considered for bitches showing aggressive behavior, keeping in mind that phenothiazines can increase prolactin secretion.

Progestins, such as megestrol acetate (Ovaban®, Shering-Plough), and androgens also suppress prolactin secretion and can diminish the clinical manifestations of false pregnancy. As would be expected, however, clinical signs often recur after progestins are withdrawn. Therefore although labeled for this use, Ovaban® is not recommended. Ovariohysterectomy should not be performed during mid- to late diestrus because false pregnancy can occur as a result of removing the ovarian source of progesterone, particularly in those animals with a prior history. When false pregnancy does occur after ovariohysterectomy, it may be more persistent than in intact bitches. Furthermore, in bitches spayed during an episode of false pregnancy, the condition may be greatly prolonged. Spaying during false pregnancy is therefore not recommended. Cabergoline treatment has been beneficial in the majority of these cases of prolonged false pregnancy.

If any signs of false pregnancy become recurrent in a spayed animal, the likely possibility of an ovarian remnant

should be considered. If signs of false pregnancy persist for longer than the expected 2 to 3 weeks, bitches should be evaluated for hypothyroidism (see Chapter 51). Primary hypothyroidism is associated with increased hypothalamic thyrotopin-releasing hormone (TRH), which can stimulate prolactin release. In some hypothyroid bitches an increased secretion of prolactin, presumably in response to increased TRH secretion, may result in excessive lactation if false pregnancy occurs. Thyroid hormone replacement therapy causes the lactation to resolve in these hypothyroid bitches.

# NORMAL EVENTS IN PREGNANCY AND PARTURITION

In the bitch and queen fertilization occurs in the uterine tubes (oviduct), where the fertilized ova then develop into morulae before entering the uterus. Early canine blastocysts enter the uterus about 8 to 10 days after ovulation. From 12 to 17 days after ovulation, embryos migrate within the uterus, ultimately becoming equally spaced within both uterine horns. Implantation is completed within 18 to 21 days after ovulation. In the queen morulae enter the uterine horns 5 or 6 days after ovulation and migrate within the uterus from days 6 to 8. Implantation is complete 12 to 14 days after ovulation.

Functional corpora lutea (CLs) are essential throughout pregnancy in the bitch and queen. The serum progesterone concentration can be used to assess corpora luteal function. After ovulation it should be greater than 5 to 8 ng/ml (approximately 16 to 25 nmol/L) and should continue to increase for the next 15 to 25 days (see Fig. 56-1). The serum progesterone concentration remains at peak levels for 7 to 14 days and then gradually declines throughout the remainder of pregnancy. In pregnant bitches a rapid, prepartum drop in the concentration to less than 2 ng/ml (approximately 6.4 nmol/L) is consistently found within 48 hours of whelping. This abrupt decline in progesterone is the result of an acute rise in prostaglandin  $F_{2\alpha}$  concentrations, which does not occur during the nonpregnant cycle. The luteal secretion of progesterone depends on both pituitary luteinizing hormone (LH) and prolactin. During the second half of the canine pregnancy, prolactin is the main luteotropic factor. A similar trend in the corpora luteal secretion of progesterone is observed in queens. As in the bitch, prolactin is luteotropic. Serum concentrations of prolactin and relaxin increase during the second half of pregnancy in bitches and queens.

Body weight and caloric needs steadily increase throughout pregnancy, especially during the last trimester, in both bitches and queens. Body weight steadily increases through weeks 4 to 7, with as much as a 40% increase in caloric intake. Appetite often declines during the last 2 weeks of pregnancy, but body weight continues to increase because of fetal and mammary growth. Weight loss does not occur during normal pregnancy. Animals that are underweight may have difficulty maintaining body condition and milk production after parturition. Conversely, obesity is known to contribute to the development of dystocia and increased neonatal mortality. In bitches the packed cell volume (PCV) declines to 40% by day 35 and to less than 35% at term. Mild, mature neutrophilia is common in pregnant bitches. Red blood cell (RBC) numbers, the hemoglobin concentration, and PCV decline throughout pregnancy in queens as well, but the absolute numbers are often still within the normal range.

# **FECUNDITY**

Overall health, body condition, nutrition, and age greatly influence fecundity. Conception rates and litter size are greatest and neonatal mortality is lowest in Beagles between 2 and 3.5 years of age. After 5 years of age, conception rate and litter size decline and neonatal mortality begins to increase. Litter size also varies with parity, with the largest litters at third and fourth parity. In the bitch litter size varies according to breed, with smaller breeds tending to have smaller litters than larger breeds. Analysis of litters registered by the American Kennel Club showed that litter size for Labrador Retrievers and Golden Retrievers ranged from five to ten pups, with 70% of the litters containing seven or more pups. Conversely, litter size for Chihuahuas and Yorkshire terriers ranged from two to five pups, with 80% of the litters having four pups or less (Kelley, 2002). In the queen litters typically consist of two to five kittens, with an average of four, irrespective of breed. Litter size and neonatal survival are best in queens 1 to 5 years of age, provided that first parity occurs before 3 years of age. Litter size and neonatal survival usually improve after first parity. If first parity occurs after 3 years of age, however, litter size and neonatal survival usually remain poor. Reproductive performance of queens declines after 6 years of age. Superfecundation, in which litter mates have different sires, commonly occurs in queens and bitches. When it does, DNA tests for paternity can be performed by various laboratories (examples: VetGen.com; VGL.ucdavis.edu).

#### **PREGNANCY DIAGNOSIS**

Pregnancy can be confirmed by palpating the abdomen, performing diagnostic imaging, and detecting the hormone relaxin in blood. Abdominal palpation is easily and quickly performed, especially in cats. Although this is the most subjective method of pregnancy diagnosis, it is a reliable method for those skilled in palpation. Palpably distinct uterine swellings that represent uterine edema, embryonic membranes, and early placental development are about 1 cm in diameter at 20 days after breeding and about 2.5 cm by day 25. By 30 to 35 days the gestational sacs are becoming elongated and the uterus is more diffusely enlarged, making it more difficult to detect pregnancy by palpation at that time. Uterine enlargement caused by pregnancy cannot be accurately differentiated from uterine enlargement caused by some other process, such as pyometra, on the basis of abdominal palpation findings alone.

Ultrasonography is an excellent method of pregnancy detection in bitches and queens. It has the advantage of also assessing fetal viability because cardiac activity and fetal movements are evident. Pregnancy can be diagnosed when the gestational sac or fetal structures are identified (see Fig. 56-9, A; Fig. 58-1). The gestational sac appears as a spherical, anechoic structure surrounded by a hyperechoic wall composed of the uterine wall and placenta. Hyperechoic fetal structures are seen within the gestational sac. Although it is possible to identify the gestational sac as early as 10 days after breeding in the bitch and queen, pregnancy is more reliably detected 24 to 28 days after breeding in bitches and 20 to 24 days after breeding in queens. At that time fetal structures and cardiac activity are detected within the gestational sacs. Fetal heart rates range from about 200 to 250 beats per minute. Fetal movement characterized by dorsiflexion of the head and extension of the limbs is common in both species after day 33 to 39. By days 40 to 50 fetal anatomy is obvious (Fig. 58-2). Nonviable fetuses show no motion and lose identifiable morphology within 1 day of death. After death the

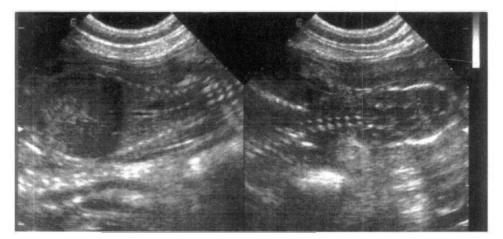


FIG 58-1
Sonograms of canine pregnancy, 40 days after first breeding (dorsal view). Fetal spine and ribs appear on left image. On right image cervical spine and outline of fetal skull are shown.

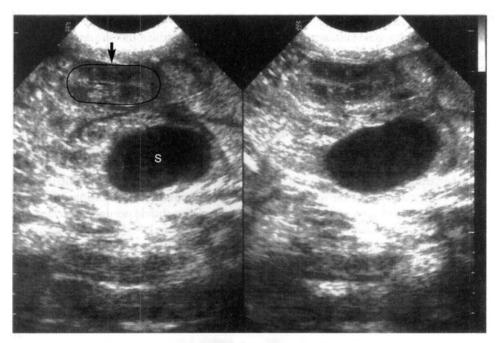


FIG 58-2 Sonogram of 59-day canine fetus. Fetal kidney (arrow) and stomach (S).

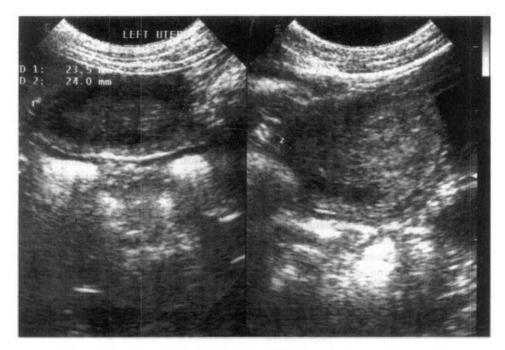


FIG 58-3 Sonogram of resorbing fetus, 30 days after first breeding.

fetal size decreases, and the fetus assumes the appearance of an ovoid mass of heterogeneous echogenicity (Fig. 58-3).

Because the hormone relaxin is produced primarily by the placenta, it is pregnancy specific in bitches and queens. In pregnant females, relaxin reaches detectable levels in serum or plasma as early as 20 days after the LH surge and peaks 30 to 35 days after the LH surge. It remains high throughout pregnancy, until parturition or abortion, when

it declines precipitously. Although relaxin can be detected 21 days after breeding, it is a more sensitive indicator of pregnancy when performed 30 or more days after breeding. Finding high concentrations of relaxin in serum or plasma confirms pregnancy. Declining or undetectable concentrations are found in cases of spontaneous or induced abortion and after parturition. Relaxin is undetectable in pseudopregnant and nonpregnant bitches and queens.

Abdominal radiography can be used to confirm pregnancy after the fetal skeleton has calcified sufficiently to be detected on radiographs. This usually happens approximately 40 to 45 days after breeding in the bitch and 35 to 40 days after breeding in the queen. Before that time the enlarging uterus appears as a tubular fluid density. Because abdominal radiographs are taken later, they are usually not used for pregnancy diagnosis per se. They are used to estimate fetal numbers, identify problems that might lead to dystocia, and confirm the remaining presence of fetuses in the bitch or queen examined because of dystocia.

#### **GESTATION LENGTH**

Gestation length, defined as the interval from a fertile mating to parturition, averages 66 days (range 64 to 71 days) in queens. Because the bitch ovulates spontaneously at any time during estrus, determining gestation length on the basis of breeding date is more variable (see Chapter 56). The average gestation length is  $63 \pm 7$  days if calculated from the date of first breeding to parturition. It is  $65 \pm 1$  days if calculated from the LH peak and  $57 \pm 3$  days if calculated from the first day of cytologically confirmed diestrus. Gestation length appears to vary somewhat according to breed of dog and the size of the litter as well. In a group of 308 large dogs (Hounds, Retrievers, German Shepard Dogs), litters of four or fewer pups averaged 1 day longer gestation than litters with five or more pups (Eilts et al., 2005). Conversely, in 36 Beagles litter size, which ranged from two to eleven pups, had no significant effect on gestation length (Tsutsui et al., 2006b).

# **PARTURITION**

Physiologically, parturition may be thought of as a release from inhibitory effects on the uterus and the recruitment of factors promoting uterine activity. Factors that maintain uterine quiescence during pregnancy include progesterone and relaxin. Factors that stimulate uterine activity include prostaglandin and oxytocin. In the bitch maternal cortisol (and probably also fetal cortisol) concentration and maternal prostaglandin PGF<sub>2α</sub> concentration increase before parturition. PGF<sub>2α</sub> causes luteolysis and a subsequent decrease in the serum progesterone concentration to less than 1 ng/ml (approximately 3 nmol/L) 24 hours before parturition. Although a similar prepartum decline in the serum progesterone concentration is seen in queens, basal concentrations are apparently not necessary for parturition to be initiated. Prostaglandin also stimulates uterine contractions, as does oxytocin. Among other mechanisms, oxytocin is released in response to pressure against the cervix. The decrease in progesterone and increase in prostaglandin cause the placenta to separate. Relaxin, which is produced by the placenta, abruptly declines at parturition. In both bitches and queens a prepartum increase in the prolactin concentration is seen, which is probably also a result of the decreased serum progesterone concentration. Postpartum, prolactin secretion is stimulated by suckling. In queens the serum estradiol concentration increases before parturition, but in the bitch  $PGF_{2\alpha}$  increases without an increase in estradiol.

#### PREDICTING LABOR

Accurate prediction of the due date is helpful in planning for normal deliveries, scheduling cesarean sections, and evaluating females with suspected prolonged gestation. Because queens are induced to ovulate by coitus, breeding date can be used to predict parturition within ±1 day of the average 66-day gestation. Using breeding dates alone, the clinician can predict parturition within ±7 days of the average 63-day gestation in bitches. A range of 14 days is too imprecise to be helpful in managing problem pregnancies. In bitches identifying the first day of diestrus on the basis of vaginal cytologic findings (see Chapter 56) can be used to predict when labor should occur because most bitches whelp  $57 \pm 3$ days after day 1 of diestrus. Parturition occurs  $65 \pm 1$  days after the LH surge in the bitch. The LH surge can be measured directly, or estimated by the concomitant initial rise above basal serum progesterone concentrations that occurs during estrus (Chapter 56). Because the serum concentrations of progesterone decrease from more than 3 ng/ml (approximately 9 nmol/L) to less than 1 ng/ml (approximately 3 nmol/L) during the 24 hours before labor in bitches, determining the prepartum progesterone concentration is very useful to determine that a bitch has reached full term.

Alternatively, because the decrease in the scrum progesterone concentration just before whelping causes a transient drop in the rectal temperature in most bitches, measuring the rectal temperature is a useful way to predict impending labor. The usual recommendation is for owners to monitor rectal temperature two to three times daily during the last 2 weeks of gestation to establish a baseline. Temperature decreases below baseline by 2° to 3° F (1.1° to 1.7° C) 6 to 18 hours before parturition. In small breeds it may drop as low as 95° F (35° C), in medium-size breeds as low as 96.8° F (36° C), and in large breeds to 98.6° F (37° C). When the drop in temperature is identified, it is usually a reliable indication that parturition will soon occur. In some bitches the temperature fluctuates. In a study of 100 canine pregnancies in which rectal temperature was taken approximately every 12 hours, the prepartum drop in rectal temperature was not detected in 19 animals before the delivery of the first pup. A prepartum drop in the rectal temperature of queens is an inconsistent finding. Many, but not all, queens refuse to eat during the last 24 to 48 hours of gestation. Loss of appetite usually is a good indicator of impending parturition.

If obvious signs of labor are not present within 24 hours of the rectal temperature drop in near-term bitches or of the loss of appetite in near-term queens, the gravid female should be examined. Unfortunately, diagnostic imaging does not add precision when estimating impending parturition. However, it is very useful for assessing fetal development and viability. Using the extent of fetal skeletal mineralization on radiographs, including the recognition of teeth and phalanges, to predict parturition was only accurate to within 3 days in 75% of cats. Using the diameter of the inner chorionic cavity and the biparietal (skull) diameter on ultrasound to predict parturition was only accurate to within 2 days in 86% of bitches.

# STAGES OF LABOR

Three stages of labor exist in bitches and queens. Stage I is characterized by nesting behavior, restlessness, shivering, and anorexia. Bitches usually pant. The cervix dilates during stage I. No external signs of uterine or abdominal contractions exist. However, uterine contractions can be documented using ultrasound or external pressure transducers (tocodynamometers) that are strapped around the belly. During pregnancy, uterine contractions are slow and tonic in nature. During stage I of parturition, uterine contractions increase in frequency, duration, and strength. These changes are coincident with the decline in progesterone concentrations, the decline in rectal temperature, and the change in behavior of the bitch. As determined by changes in rectal temperature and change in the dam's behavior, stage I normally lasts for 6 to 12 hours. As determined by the change in uterine contractions until the delivery of the first pup, the duration of stage I was reported to be 13 to 24 hours in one study (n = 5 bitches) and to average 12 hours in another (n = 100 bitches) (Copley, 2002).

Stage II is characterized by obvious abdominal contractions, passage of amnionic fluid, and delivery of the puppy or kitten. Rectal temperature is normal or slightly above normal. Stage II is usually accomplished in 3 to 6 hours. It may last as long as 12 hours in some normal bitches. In some normal queens it may rarely last 24 hours. There may be intermittent, active abdominal straining for several hours before the birth of the first neonate. Constant, unrelenting straining is not normal. Usually less than 1 hour passes between the delivery of subsequent puppies or kittens. The dam may rest for as long as 1 hour or so between births, with no active straining during that time. Occasionally, 12 to 24 hours pass between the births of apparently healthy kittens, but this is not normal for puppies and may be associated with neonatal mortality in both species.

The placenta is normally passed within 5 to 15 minutes of the birth of each neonate. This is stage III. The dam removes the amniotic membranes and cleans the neonate, severing the umbilical cord and eating the placenta. If the dam fails to remove the fetal membranes from the neonate's face, the owner should do so. Cleaning the neonate is important maternal behavior necessary for bonding between the dam and her offspring; thus the dam should be encouraged to do it. All placentas should be passed within 4 to 6 hours. If the owner is attending, the umbilical cord should be clamped and cut about 1 cm from the body wall. If bleeding occurs, the cord can be ligated.

#### DYSTOCIA

Dystocia, or difficult birth, has an estimated overall prevalence of approximately 5% to 6% of pregnancies in bitches and queens. In certain breeds, however, the prevalence is much higher, approaching 18% in Devon Rex cats in the United Kingdom and 100% in English Bulldogs in the United States. With the exception of those breeds at high risk, dys-

tocia might be considered a relatively uncommon cause of morbidity or mortality in bitches and queens, accounting for fewer than 1% of emergency admissions. However, it is the most common periparturient problem requiring emergency care and a major cause of neonatal mortality in puppies and kittens. Overall mortality rates from birth to weaning average 12% (range 10% to 30%) in puppies and 13 % in kittens, but 65% of those losses occur at parturition and during the first week of life as a result of stillbirth, fetal stress, and hypoxia related to parturition.

There appears to be an increased risk of dystocia in aged bitches, but no relationship between age and dystocia has been found in queens. In both dogs and cats purebred animals are more likely to have dystocia than are mixed breeds. Dolicocephalic (e.g., Siamese type) and brachycephalic (e.g., Persian type) are at greater risk for dystocia than mesocephalic (e.g., domestic shorthair type) cats. In dogs chondrodysplastic breeds and those selected for large heads are at greater risk. When normal parturition is used as a criterion in selection of breeding bitches or queens, the occurrence of dystocia within the colony can be decreased, demonstrating that breed alone is not the determinant. The majority (71%) of privately owned queens presented for dystocia have experienced dystocia during more than one pregnancy, whereas in a large commercial colony of domestic shorthair cats, the incidence of dystocia was only 0.4%. This could reflect different husbandry practices or genetics of brood stock selected on the basis of reproductive performance.

The two most common causes of dystocia in small animals are (1) uterine inertia and (2) fetal malpresentation. Of these, uterine inertia is by far the most common, accounting for about 60% of all cases. Uterine inertia is the failure to develop and maintain uterine contractions sufficient for normal progression of labor. Uterine inertia has a variety of potential causes (e.g., genetic factors, age, nutrition, metabolic factors), but the specific cause for a particular case usually is not identified. The exception is mechanical obstruction that results in myometrial exhaustion and secondary uterine inertia. Fetal malpresentation accounts for approximately 15% of dystocia cases in bitches and queens.

Maternal causes of obstructive dystocia relate primarily to abnormalities in size or shape of the pelvic canal. These abnormalities may be congenital or acquired, involving the bony or soft tissue structures. Within breeds, certain individuals are at greater risk than others. For example, in both the Boston Terrier and Scottish Terrier, breeds with distinctly different head conformation, bitches with a dorsoventral flattening (i.e., vertical diameter ≤ horizontal diameter) of the pelvic canal are more likely to have obstructive dystocia than bitches with normal pelvic conformation (i.e., vertical diameter > horizontal diameter). Cephalopelvic disproportion, in which the fetal head is too large for the small maternal pelvic canal, also can occur. Uterine torsion is also a cause of obstruction (Fig. 57-9). Malpresentation is the most common fetal cause of obstruction. Fetal oversize or congenital deformities causing large abnormal shape (Fig. 58-4) may also cause obstruction.



**FIG 58-4 A,** Cause of dystocia: newborn Cardigan Welsh Corgi puppy with anasarca (ventral view). **B,** Dorsal view of same puppy with normal litter mate.

Small litter size predisposes to dystocia in bitches for a variety of reasons. The fetal signals that initiate parturition may be insufficient in very small litters, which may lead to prolonged gestation. A negative correlation between litter size and puppy size exists: the smaller the litter, the larger the individual pup. This may increase the likelihood of obstruction. Conversely, a very large litter may overstretch the uterus and lead to inertia. Litter size has no apparent bearing on the occurrence of dystocia in queens. Fetal death accounts for 1% to 4.5% of dystocia in bitches and queens, respectively. Extreme anxiety reportedly inhibits normal progression of labor. How often this contributes to dystocia in dogs and cats is not known.

## History

Early recognition and correction of dystocia is crucial to the successful management and optimal neonatal health. The first things that should be determined are the presence of placental membranes or fetal parts at the vulva, and the presence and character of any vulvar discharge. A partially delivered puppy or kitten needs immediate attention. The history should continue with an investigation of the length of gestation, known predisposition to or previous occurrence of dystocia, the progression through the stages of labor, and any indication of illness in the dam. This would include information on rectal temperature monitoring, behavior of the dam, presence and characterization of contractions, number of puppies or kittens already born, and the duration of each of these events. Breeders should be asked if they have already administered any drugs or performed any obstetric procedures. Any sign of illness in the pregnant female is reason to recommend that she be examined. On the other hand, a common error made by owners and veterinarians is to delay intervention because the dam does not appear to be in trouble. The decision to delay is usually made without regard to the well-being of the fetuses, which are often severely stressed long before the dam shows clinical signs relating to the demise of her fetuses. The dam should be examined if the expected due date has arrived and no signs of labor exist, irrespective of a lack of maternal discomfort or illness. This is to ensure that all is well with the fetuses and to determine if continued watchful waiting is a reasonable approach.

If stage I has not progressed to stage II within 12 hours, the dam should be examined, even if other signs of labor or maternal illness are lacking. Exercise often stimulates abdominal contractions. For that reason, some veterinarians have recommended that the owners walk the bitch up and down the stairs or around the house before loading her in the car for the drive to the veterinary hospital. The onset of stage II of labor is recognized by the return of rectal temperature to normal, the presence of strong abdominal contractions, and the passage of amnionic fluid. The passage of amnionic fluid is an indication of stage II labor, irrespective of contractions. The first pup should be born within 2 to 3 hours of amnionic fluid. Other findings of concern are the presence of a vulvar discharge, fetal membranes, or a partially delivered fetus (Box 58-1). Partially delivered puppies or kittens need prompt attention if they are to survive. A dark-green discharge in bitches or red-brown discharge in queens originates from the placenta. Its presence indicates that at least one placenta has begun to separate. If a pup or kitten has not been delivered within 2 to 4 hours, the dam should be examined. A bright yellow vulvar discharge is meconium. Passage of meconium is indicative of severe fetal stress. It is often associated with fetal aspiration of amnionic fluid and a grave prognosis for neonatal survival. A purulent discharge may be found if uterine infection or fetal maceration exists. Viable fetuses may also still be present.

It has been shown in dogs that neonatal mortality is directly correlated to duration of labor (Linde-Forsberg, 2005). For example, one study found that if delivery was complete within 1 to 4.5 hours of the onset of stage II labor, puppy mortality was 5.8%, whereas neonatal mortality was 13.7% after 5 to 24 hours of stage II labor. The outcome for the bitch and the puppies is favorable when the dam is healthy, the fetal heart rates are normal (>200 bpm), stage I



Indicators of Dystocia

Any sign of illness in full-term female
History of previous dystocia
Known predisposition to dystocia
More than 24 hours since rectal temperature drop in full-term bitch

More than 24 hours of anorexia in full-term queen Abnormal vulvar discharae

Failure to progress from stage I to stage II after 12 hours Partially delivered fetus for more than 10 or 15 minutes More than 3 hours of stage II labor before birth of first neonate

More than 1 hour of active labor between births Constant, unrelenting, unproductive straining of 20 to 30 minutes

Labor appears to have stopped before entire litter delivered

is less than 6 hours in duration, and the duration of stage II is less than 12 hours. When stage II lasts longer than 12 hours but less than 24 hours, the prognosis for puppy survival is poor, although the prognosis for the bitch is still fine. If stage II lasts longer than 24 hours, the puppies are likely to die and morbidity for the bitch is increased. Fetal heart rates less than 150 to 160 bpm or illness in the bitch is also associated with worsening prognosis. In a different study puppy mortality from birth to 7 days of age decreased from 33% to 6% as a result of fetal monitoring and early intervention during parturition (Davidson, 2001). Among the multiparous bitches in that study, neonatal mortality decreased from 42% to 12%.

Weak, intermittent straining lasting more than 2 to 4 hours before the first puppy or kitten is born or lasting longer than 1 hour between births is cause for concern. Strong, persistent straining lasting longer than 20 to 30 minutes without delivery of a pup or kitten is not normal. If more than 12 hours of stage II have elapsed or, conversely, if labor appears to have stopped before the entire litter is delivered, the dam should be examined. Cats have been observed to deliver live kittens over 24 to 40 hours, with no obvious straining or discomfort between kitten births. Even though live kittens are often born, such prolonged delivery is associated with increased neonatal morbidity and mortality and therefore should probably not be considered normal. The average duration of labor was reported to be 16 hours in one colony, but kitten mortality was 29%.

# **Diagnosis**

The historical and physical findings are diagnostic of dystocia. The first step is to examine the perineum for evidence of a partially delivered fetus, which requires immediate attention. There may be a bulge in the perineum dorsal to the vulva, or there may be fetal limbs or tail protruding from the vulva. When it is determined that no partially delivered

fetus is present, the complete physical examination of the dam proceeds as usual. Systemic illness in the dam should be pursued as usual for any ill animal. For example, hyperthermia may be caused by the exertion of labor, but infection, especially of the mammae or uterus, should be considered. A complete blood count (CBC) and biochemical panel would be reasonable. Regardless of cause, dehydration must be corrected.

The abdomen is palpated to evaluate uterine size, tone, and the presence of fetuses. Fetal movement and uterine contractions may be felt, but their adequacy cannot be assessed by palpation alone. The inability to detect movement or contractions via abdominal palpation is not necessarily cause for concern. The perincum is examined for the presence and character of any discharge. In bitches of adequate size a digital vaginal exam should be performed to assess for the presence of a fetus in the birth canal. If one is found, it should be delivered immediately. If none is found, the dorsal wall of the vagina should be stroked because doing so often stimulates abdominal contractions. This procedure has been referred to as feathering. The cervix is not palpable per vaginum. Puppies or kittens stuck in the vagina may be delivered by obstetric manipulation or with the aid of episiotomy. The mammary glands are palpated to assess the presence and character of secretions. Some primiparous bitches may not have obvious milk. Lactation begins within 24 hours of parturition. Multiparous bitches and queens may lactate during the last week of gestation.

After assessing maternal health by physical examination, the clinician assesses the fetuses using radiology and ultrasonography. The number, size, shape, location, posture, and presentation of any remaining fetuses are often best determined by radiographs. A cause for obstruction, such as large fetus, an abnormal pelvic canal, or fetal malposition may be identified. Fetal viability is difficult to assess on radiographs because postmortem changes are not detectable for hours or days after death (Box 58-2). Intrafetal gas may be detectable as early as 6 hours after death. The bones of the fetal skeleton and head may collapse as early as 48 hours after death. However, the absence of those radiographic signs is not diagnostic of life or death. The number of fetuses remaining cannot be accurately determined with ultrasonography; however, ultrasonography is ideal for assessment of fetal viability on the basis of heart rate and fetal movement.

As determined by ultrasound, normal canine fetal heart rates during labor are 170 to 230 bpm. Fetal kittens' heart rates are 190 to 250 bpm. Fetal movement is observed from about day 40 of gestation onward. Normal fetuses are quite active near term. Subjectively, this activity seems to increase during ultrasonographic examination. Fetal movement and heart rates are decreased as a result of stress and hypoxemia. In fetal pups heart rates below normal are associated with poor neonatal survival unless pups are delivered promptly. It has been shown that heart rates < 150 to 160 bpm indicate fetal stress. When heart rates are less than 130 bpm, there is poor survival unless pups are delivered within 1 to 2 hours. There is high neonatal mortality among pups with fetal



BOX 58-2

#### Radiographic Signs of Fetal Death

Absence of continued uterine enlargement before fetal skeletons are detected

Absence of continued fetal growth after initial detection of fetal skeletons

Demineralization or inadequate mineralization of fetal skeleton for gestational age

Overlap of skull bones, collapse of axial skeleton, or misalignment of fetal bones

Intrauterine or intrafetal gas

heart rates less than 100 bpm unless they are immediately delivered. We have also observed that lack of fetal movement, irrespective of heart rate, is also a poor prognostic indicator. Presumably, the situation is similar in cats, taking the normally faster feline heart rate into account. The precise gestational age cannot be determined on the basis of ultrasonographic findings, but fetal maturity and impending fetal death can be assessed by the development, or lack thereof, of fetal organs (see Fig. 58-2). Previously recognizable fetal anatomy begins to be lost within 24 hours of fetal death. The overall size of the fetal mass decreases and condenses into a heterogeneous echotexture (see Fig. 58-3).

# **Treatment**

A partially delivered fetus should be delivered within 10 minutes. Care must be taken to avoid disarticulating the extremities. Liberal amounts of lubrication should be used. Rotating the fetus 45 degrees to take advantage of the widest diagonal part of the pelvic canal may be helpful. Gently alternating traction from left to right (i.e., rocking) may help relieve shoulder or hip lock. Traction should be applied in a ventral direction that follows the natural conformation of the vestibule. It may be helpful to lift the vulvar lips upward while pressing the pup downward. A vaginal exam should be performed in all dams of adequate size to determine whether a fetus is lodged in the vagina and to stimulate the vagina (i.e., feathering) in hopes of initiating abdominal contractions. If the dam is extremely nervous, mild sedation should be considered.

When the clinician has determined that an "overdue" bitch is healthy and the fetuses are healthy (as determined by the presence of fetal movement and normal heart rates), serum concentrations of progesterone may be determined. This would be especially helpful when information by which the actual length of gestation might be calculated is lacking. The finding of progesterone that is greater than 3 ng/ml (9 nmol/L) in a bitch would indicate that the pregnancy has not yet reached full term. Intervention should be delayed, and watchful waiting should continue for several hours. If 24 hours pass with no progression of labor, all parameters should be reassessed. Aglepristone, 15 mg/kg, given subcutaneously twice on 1 day, safely and effectively induced parturition in Beagle bitches (Baan et al., 2005). Progesterone

concentrations were still elevated when treatment began. Parturition occurred 32 to 56 hours (mean 41 hours) after the first injection. Puppy survival rates were no different from those of control bitches that whelped naturally. The only side effect was irritation at the injection site.

Animals in stage I of labor are expected to progress to stage II in less than 12 to 24 hours. When that does not happen, watchful waiting no longer applies, nor does it apply to dams already in stage II of labor. Sometimes, all other parameters are found to be normal except one of the fetuses is not moving or has a heart rate of 150 to 160 bpm or less. The dam and the other fetuses are healthy. In that situation the benefits of immediate intervention in an attempt to save all the fetuses should be weighed against the cost and risks. For example, the decisions made in a situation in which all but one of 10 puppies are apparently normal might be different from the decisions made under identical circumstances but a litter size of only two. The owner's attitude about the relative value of each puppy or kitten in the litter and about stillbirth or neonatal death must be considered. It is common for bitches and queens to carry healthy fetuses to term despite the death of some litter mates.

The type of treatment is dictated by the presence or absence of obstruction and by the health of the dam and fetuses. If obstruction or serious fetal compromise exists, cesarean section is indicated without delay. If no obstruction exists, medical management may be attempted in healthy dams with no signs of fetal stress. Several studies have found that 65% to 80% of bitches and queens presented for dystocia were eventually treated with cesarean section. Medical management was successful in resolving the dystocia in only 20% to 30% of canine and feline cases. The maternal mortality rate is reported to be about 1% among bitches undergoing cesarean section. In addition to maternal survival, the goal of managing dystocia is to achieve puppy and kitten survival beyond the most critical first week of life.

When the dam and the fetuses are healthy and no obstruction exists, medical management of dystocia can be considered. The goal of medical management is to reestablish a normal labor pattern of uterine contractions. This is done with oxytocin and calcium. Typically, oxytocin increases the frequency of uterine contractions and calcium increases the strength. High doses and/or frequent administration of oxytocin are contraindicated because they cause sustained uterine contractions that delay the expulsion of fetuses and compromise placental blood flow. This causes placental separation, fetal hypoxia, and fetal acidosis. These actions contribute to fetal and neonatal mortality. The goal of oxytocin therapy is to increase the frequency of uterine contractions to a normal labor pattern. This is best accomplished while the uterine contractions are being monitored. Unfortunately, this is often not done in veterinary medicine. Studies in which uterine monitoring was done have demonstrated that the large doses of oxytocin that have traditionally been recommended are not necessary. Current recommendations are to administer small doses, 0.25 to 4.0 U per dog, intramuscularly. In our colony of mixed-breed dogs weighing 35 to 45 lb, we administer 0.25 U. We do not monitor uterine pressure. Labor should progress (i.e., straining begins) within 30 minutes, and a pup should soon be delivered. If so, the clinician may repeat administration of oxytocin as needed to perpetuate normal parturition. Repeated doses should not be administered if a normal labor pattern is not established. In studies that monitored uterine contractions of whelping bitches, the mean total cumulative doses of oxytocin needed were 4 to 7.7 U per bitch. When the animal does not respond to oxytocin administration within 30 to 45 minutes, it is unlikely that further treatment with single agent oxytocin will be beneficial.

Myometrial contraction depends on the influx of calcium ions. Generally speaking, calcium administration increases the strength of uterine contractions even in the absence of documented hypocalcemia. For this reason some clinicians have recommended the routine administration of calcium gluconate in the management of nonobstructive dystocia. It has been recommended by some that 10% calcium gluconate be administered before the administration of oxytocin. If normal labor does not resume, oxytocin is added. Calcium gluconate 10%, 0.2 ml/kg or less, or 1 to 5 ml/dog, is administered subcutaneously or intravenously depending on the preparation and the label directions. Some preparations are too irritating to be administered by routes other than intravenous (IV). If the IV route is chosen, calcium is administered slowly (1 ml/min) while monitoring the heart. Administration should be immediately discontinued if bradycardia or dysrhythmia occurs. If labor progresses (i.e., straining begins), calcium may be repeated as needed or continued with oxytocin. In a study using uterine monitoring as a guide, the mean total cumulative dose of 10% Ca gluconate administered to bitches was 3 ml. Conversely, before uterine monitoring was available, doses of 1.5 to 20 ml were reported. Higher doses or bolus IV administration of Ca gluconate should be reserved for animals with documented clinical signs or laboratory evidence of hypocalcemia. When medical management fails to initiate a normal labor pattern, cesarean section should be performed without delay.

Cesarean section is indicated, without delay, in the following circumstances: obstruction, such as fetal oversize, fetal malposition, or uterine torsion; existence of fetal compromise; failure of medical management with calcium and oxytocin administration; the possibility that continued pregnancy or labor might be harmful to the bitch or queen; or preexisting maternal illness. At the time of this writing, at least one company provides fetal and uterine monitoring services for veterinarians: Veterinary Perinatal Specialties (www.whelpwise.com).

# PREGNANCY LOSS

# Etiology

Infectious disease is an important cause of pregnancy loss in dogs and cats. Infectious diseases can cause early embryonic

death, resorption, or abortion through their effects on the dam, the fetus, or the placenta. Other than interrupting pregnancy, many of these pathogens cause minimal clinical signs of maternal illness. Bacteria reported to cause fetal death and abortion in bitches include *Brucella canis, Escherichia coli*, β-hemolytic *Streptococcus, Leptospira, Campylobacter, Salmonella, Mycoplasma* spp., and *Brucella abortus*. Bacterial causes of pregnancy loss are uncommonly reported in cats. Experimental infection with *Toxoplasma gondii* has also been found to cause abortion in bitches and queens.

# **Clinical Features**

Embryonic and fetal death can result from maternal disorders, fetal disorders, or placental disorders. Queens and bitches often lose one or more fetuses and yet carry the rest of the litter to term and deliver normal healthy puppies or kittens. Anything that adversely affects the health of the dam and medications used for treatment have the potential to adversely affect the pregnancy. Other than a disorder that causes overt clinical illness in the dam, the signs associated with fetal death depend primarily on the stage of gestation at which the loss occurs.

When early embryonic death occurs, there are no clinical signs of the bitch having been pregnant. Therefore the bitch is likely to be presented for (apparent) failure to conceive rather than for pregnancy loss. In pregnant queens, early embryonic death will be reflected by a prolonged interestrual interval of 30 to 50 days rather than the usual nonovulatory cycles every 14 to 21 days. Pregnancy loss has no effect on the canine interestrual interval because the canine CLs persist for more than 60 days regardless of whether the bitch is pregnant. Progesterone, produced by the CLs, causes mammary development and weight gain regardless of whether pregnancy exists. Therefore bitches may continue to appear pregnant for 60 or more days. If early pregnancy is lost in queens, the CLs regress in 30 to 50 days; thus any appearance of pregnancy diminishes after that time. Other than the loss of mammary development in queens, usually there are no physical signs, such as vulvar discharge, when embryonic death occurs during the first 30 days of gestation in bitches and queens. Resorption occurs. When fetal death occurs after about day 30 of pregnancy, uterine contents are passed (abortion). The first clinical sign of abortion is usually a blood-tinged vulvar discharge. The character of the discharge is variable, according to the underlying cause of the abortion. The quantity is variable from scant to substantial. The later in gestation fetal death occurs, the more obvious it becomes that fetal parts are being expelled.

#### MYCOPLASMA

Mycoplasma and Ureaplasma are members of the normal florae in the canine vagina, prepuce, and distal urethra. Mycoplasma has been isolated from 59% of vaginal cultures, 80% of preputial samples, and 27% of semen samples from normal dogs in kennels with excellent pregnancy rates of 88% to 90%. Mycoplasma infection has been reported to cause conjunctivitis, polyarthritis, abscesses, and urinary

tract infection in cats. In dogs pneumonia, urinary tract infection, colitis, and reproductive disorders have been associated with *Mycoplasma* and *Ureaplasma* infection. Although experimental inoculation of the reproductive tract with *Mycoplasma canis* causes endometritis in bitches and orchitis and epididymitis in dogs, the significance of *Mycoplasma* in spontaneously occurring canine reproductive disease is unclear because there is no difference between the prevalence of *Mycoplasma* isolated from normal animals and the prevalence of *Mycoplasma* isolated from animals with reproductive disorders.

Because Mycoplasma and Ureaplasma are members of the normal canine genital florae and because they are isolated with equal frequency from normal dogs and dogs with reproductive disorders, Mycoplasma or Ureaplasma infection should not be diagnosed on the basis of culture results alone. The clinical signs and cytologic findings should also be consistent with an infectious process. Mycoplasma and Ureaplasma are fragile organisms. A special medium such as Amies should be used for culture studies, and samples should be placed on ice and arrive at the laboratory within 24 hours. Susceptibility testing is rarely available. Usually, the organisms are susceptible to tetracycline, chloramphenicol, and fluoroquinolones. Unfortunately, many of these antibiotics are contraindicated during pregnancy and lactation. Isolation and even culling of infected animals have been recommended for the control of Mycoplasma infection in a kennel, but such extreme measures are not usually necessary.

# **BRUCELLA CANIS**

Brucella canis is a small, gram-negative coccobacillus. Dogs are the definitive host for *B. canis* infection. They are much less susceptible to *Brucella abortus* and *Brucella suis*. Cats are resistant to *B. canis* but can be infected under experimental conditions. Compared to *B. abortus* and *Brucella mellitensus* infection, people are relatively resistant to *B. canis*. The source of infection is usually the person's own pet. Laboratory personnel have also acquired the disease from infected specimens. Biohazard precautions should be taken when handling specimens from suspect animals. The prevalence of human *B. canis* infection in the United States is not known because although human brucellosis is a notifiable disease, the Centers for Disease Control (CDC) does not require speciation. In one study *B. canis* infection accounted for 4 of the 331 people with brucellosis in a 10-year period.

B. canis readily crosses all mucous membranes. Although venereal transmission occurs, the most common routes of infection are oronasal and conjunctival. Neutered and "virgin" animals can become infected as well as sexually intact animals. The greatest numbers of organisms are shed in aborted material and postabortion vaginal discharge, which readily contaminate the environment. Large numbers are shed in semen, particularly during the first 6 to 8 weeks of infection, but shedding persists for 60 weeks to 2 years. Organisms are also shed in urine, especially from males. Urinary shedding persists for at least 3 months. Urine is

especially important in transmission when animals are housed in groups. *B. canis* is shed in milk, and transplacental transmission occurs. It can also be transmitted on contaminated fomites.

Tissue macrophages and other phagocytic cells carry the organism to lymphoid tissue, bone marrow, and the reproductive tract, where they multiply. Organisms persist in mononuclear phagocytes, bone marrow, lymph node, spleen, and prostate. Persistence of the organism in the prostate is thought to explain the greater number of organisms recovered from the urine of infected males than from females. Bacteremia is present 1 to 4 weeks after infection and persists for 6 months to 5.5 years. Nonprotective antibodies develop within weeks of infection but may not be detectable until 8 to 12 weeks after inoculation. Titers persist for as long as the bacteremia is present. Titers decline after the bacteremia subsides, even though the organism is still present in tissues.

#### **Clinical Features**

B. canis infection primarily affects reproduction. Transient lymphadnopathy may be observed. Animals are afebrile. Placentitis caused by B. canis results in fetal death. Abortion after about day 45 is the most commonly reported clinical sign of B. canis infection in females. However, fetal death may occur at any time during gestation, and early embryonic death would go unnoticed or could be misinterpreted as conception failure. Occasionally, a litter is carried to term, but the pups usually die within a few days of birth.

The most common clinical sign of B. canis infection in males is infertility. Scrotal and epididymal enlargement are usually transient early in infection. Testicular enlargement is uncommon. Abnormalities in seminal quality occur within 5 weeks of infection and become pronounced by 8 weeks. White blood cells, macrophages, sperm agglutination, and abnormal sperm morphology are found. By 20 weeks of infection, more than 90% of the sperm may be abnormal. Eventually, testicular atrophy and azoospermia develop, and inflammatory cells are no longer found in semen. Other than reproductive signs, dogs are healthy. B. canis may infect nonreproductive organs, most notably the eye and intervertebral disk. In such cases there are clinical signs associated with uveitis and discospondylitis. Osteomyelitis, dermatitis, meningoencephalitis, and glomerulonephropathy are less common.

# Diagnosis

The diagnosis of *B. canis* infection is suggested by the history of abortion in females, infertility and seminal abnormalities in the male, and the relative absence of physical abnormalities. The diagnosis of *B. canis* is confirmed by identification of the organism by culture or polymerase chain reaction (PCR). Positive serologic results must be confirmed by these methods. Blood, postabortion vaginal discharge, and semen are the best specimens for culture. Blood culture or PCR is the best method for identifying early (2 to 8 weeks) infection. The number of bacteria in blood usually remains very high for at least 6 months after infection. Bacteremia subsides as

the infection becomes chronic; thus blood cultures are not always positive. Semen cultures are most helpful during the first 3 months of infection, when the number of organisms in semen is high. Urine cultures may be positive, especially in males. The organism can also be recovered from lymph nodes, spleen, liver, bone marrow, prostate, epididymis, placenta, and the lumen of the gravid or postabortion uterus. *B. canis* is rarely recovered from the nonpregnant uterus or the vagina except after abortion.

Although isolation of the organism is the definitive diagnosis, it is impractical for the routine screening of asymptomatic animals. For this reason serologic testing is the most frequently used screening diagnostic procedure for *B. canis* infection. Antibodies to cell wall (somatic) lipopolysaccharide (LPS) antigens of *B. canis* cross-react with many other organisms including *Pseudomonas aeruginosa*, *Staphylococcus*, *Actinobacillus equuli*, and *Brucella ovis*. Therefore any of the serologic tests using cell wall LPS antigens have high false-positive rates, some as high as 60%. The addition of 2-mercaptoethanol (2-ME) eliminates the less specific reactions of IgM antibodies, but false-positive results are still common. Internal cytoplasmic protein antigens (CPAg), on the other hand, are highly specific for *Brucella* infection.

Serologic tests using cell wall antigens include the following: 2-ME rapid slide agglutination test (RSAT), 2-ME tube agglutination test (TAT), indirect fluorescent antibody (IFA), agar gel immunodiffusion (AGID), and enzymelinked immunosorbent assay (ELISA). The serologic tests that include the more specific cytoplasmic protein antigen are the AGID (CPAg) at NYS Diagnostic Laboratory, Cornell University, Ithaca, New York, and an ELISA (CPAg) that has limited availability. Unfortunately, laboratory reagents and/or methods have not been standardized for any of these tests except 2-ME RSAT and 2-ME TAT. Availability of the standardized reagents for 2-ME TAT is sporadic. Therefore the reliability of test results and the accuracy of interpretation are extremely variable among laboratories.

Despite its lack of specificity the RSAT (D-Tec CB®; Synbiotics) has the tremendous advantage of being easy, quick to perform, and highly sensitive. Negative RSAT results are rare (1%) in animals that have been infected long enough to develop detectable antibodies (8 to 12 weeks). Treatment with antibiotics causes negative culture and serology results, despite persistence of the organism in tissues. Titers decline in chronic infection, but they may persist for months after the bacteremia has ceased.

#### **Treatment**

Antibiotic therapy rarely, if ever, results in a cure for *B. canis* infection. The results of cultures and serologic testing become negative in animals with chronic infection and also in those receiving antibiotic therapy, despite the persistence of *B. canis* in tissues; thus it is difficult to ascribe declining titers or negative culture findings to treatment rather than to the natural progression of the disease. Bacteremia and positive serologic results often recur days to months after treatment. Minocycline, tetracycline, dihydrostreptomycin,

trimethoprim sulfadiazine, gentamicin, doxycycline, enrofloxacin, and various combinations thereof have been used to treat *B. canis*. The vast majority of treated dogs remained infected. Evidence shows that, despite therapy, the organism is not cleared from the prostate. Testicular damage is usually irreversible. Treated dogs are readily susceptible to reinfection. Because the chance of successful treatment is so unlikely and because infected animals remain a source of infection for other dogs and people, treatment is ill advised. If treatment is attempted, infected animals should be neutered to minimize the shed of organisms. No vaccine exists.

## **Prevention and Control**

B. canis is insidious. No readily recognizable signs appear until animals have been infected for weeks or months, during which time they have exposed other members of the colony to the infection. Eventually, B. canis infection will devastate the reproductive performance of the individual animal and the kennel. In kennels with infected animals, conception rates can decline to as low as 30%; the proportion of pregnancies ending in abortion can reach 80%; litter size (Beagles) can decline from a previous average of six pups to one pup per litter; and the number of pups surviving to weaning age can reach zero. Obviously, the risk of inadvertent exposure to asymptomatic, infected animals that are brought into the colony, even briefly, is too great to leave to chance. All animals should be tested before breeding. New members to be added to the colony should be quarantined for 8 to 12 weeks until the results of at least two tests performed at 4-week intervals are negative. Animals with any of the symptoms of B. canis infection should never be admitted to the colony for any reason until B. canis infection is positively excluded as the cause. As with asymptomatic animals, it may take as long as 3 months to ensure that the animal is not infected.

The RSAT is recommended for the routine screening of asymptomatic animals because it is so sensitive. If the animal has been infected for 8 to 12 weeks so that antibodies have reached detectable levels, if the animal is not so chronically infected that the titers have declined, and if no antibiotics have been administered, animals that do not have the infection should be correctly identified by a negative test result. Positive test results must be confirmed with other methods because the RSAT lacks specificity and false-positive results are common.

When an animal is found to be positive on the basis of the RSAT or other screening test, especially if clinical signs compatible with *B. canis* infection are seen, the animal should be isolated from the rest of the colony and the entire kennel should be quarantined until the results can be verified. The definitive diagnosis can be made only on the basis of the isolation and identification of the organism from culture or PCR of appropriate specimens. An AGID test that uses CPAg, but not those using LPS antigen, may also be helpful to confirm the diagnosis.

When the infection is confirmed, the positive animal should be eliminated from the colony and all other colony members tested monthly. All positive animals are eliminated.

Monthly colony-wide testing of all remaining animals, including those with negative results to the previous month's test, continues until all results are negative in all the remaining animals for 3 consecutive months. Because of the biologic behavior of the infection, it is expected that additional positive animals will be found for several months. Therefore the prevalence of infected animals in the colony is usually not significantly lowered until testing and culling have continued for 4 to 5 months.

Testing and culling are time-consuming and expensive, even in small colonies. Many are tempted to try treating the disease rather than to accept the immediate losses incurred by culling. Treatment is made all the more attractive by reports of apparent success. Bacteremia and serologic titers diminish in response to antibiotic therapy, and many treated bitches successfully conceive and carry a healthy litter to term during that time. However, evidence from studies in which animals were evaluated by culturing internal organs or blood 6 or more months after treatment shows that many still harbor the organism despite negative serologic test results. Thus far, the evidence of all the studies of spontaneously occurring infection have shown that B. canis is not eliminated from the colony, even when infected animals are strictly isolated and regardless of treatment, until infected animals are actually culled.

A different approach might be considered for a household pet than for a breeding animal. Antibiotic therapy plus neutering should essentially eliminate genital secretions and the shedding of organisms by this route, but not necessarily others. Treatment and neutering would not absolutely exclude the possibility that the animal might remain a source of infection for other dogs or human members of the household. Owners of pets or kennels should be informed of the zoonotic potential. All people exposed to infected or suspect animals should practice good hygiene.

## **HERPES VIRUS**

Herpes virus has been implicated as a cause of abortion, stillbirths, and infertility in dogs and cats. Canine herpes virus (CHV) has been suggested as the causative organism of vesicular lesions of the vagina and prepuce, but isolation of the virus from spontaneously occurring genital cases is rarely reported. Mild respiratory tract disease is by far the most common clinical sign of herpes virus infection in dogs and cats older than 12 weeks of age. The lesions are usually limited to the mucosal surfaces of the oropharynx. Occasionally, the manifestations of feline herpes virus (FHV) type I (i.e., rhinotracheitis) may be severe and include conjunctivitis, corneal ulceration, and fatal pneumonia. In neonates herpes virus infection causes fulminant multiple-organ failure and death. Neonates become infected in utero, through exposure to infected secretions of the dam, or through postnatal exposure to infected older members of the colony. Neonatal herpes virus infection is one of the most common manifestations of CHV infection in a breeding colony. Neonates nursing from seropositive bitches are resistant to infection.

Because herpes viruses are spread primarily by aerosolization and direct contact with oronasal secretions, the population density, segregation of life stages, and sanitation of the facility influence the severity of disease within the colony. The prevalence of CHV is estimated to be 10% to 15% in single-pet households and as high as 85% in kennels. Once infected, animals are considered infected for life. The infection may remain latent or be expressed at any time. Nasal secretions, even from asymptomatic carriers, are considered epizootiologically the most important routes of transmission. Venereal transmission of CHVs and FHVs is rare.

# Diagnosis

The most common clinical signs of herpes virus infection in dogs and cats are respiratory. From the standpoint of reproductive disease, herpes virus infection should be considered in cases of acute neonatal death, as a potential cause of abortion in dogs and cats, as a potential cause of infertility in cats, and as a potential cause of vesicular lesions of the mucosal surfaces of the genitalia in adult dogs. The diagnosis can be confirmed by the finding of the characteristic intranuclear inclusion bodies in tissue sections, by serologic studies, and by virus isolation and PCR.

Swabs from the affected area (genital lesion, conjunctiva, nasal) should be submitted on ice for virus isolation. Some laboratories have found that herpes viruses are more easily recovered from rayon-Dacron swabs (Dacron-tipped applicators; Baxter) than from wooden cotton-tipped swabs. This is especially important if the virus concentration is low. Herpes virus has usually not been isolated beyond 2 to 3 weeks after the primary infection. Therefore virus isolation is not a very useful diagnostic test for chronic infection, unless viral recrudescence has occurred. Herpes viruses induce a weak systemic humoral response in the host, with antibody titers rising and falling quickly (4 to 8 weeks) after infection. If seropositive animals also show typical clinical signs, this is considered diagnostic for herpes virus infection. Suspected herpes-induced genital lesions can be biopsied. Histopathologic findings typical of herpes virus infection include the vesicles, degeneration of epithelial cells, and marked acantholysis. Intranuclear inclusions may be found but are less common in the material from genital lesions than in nasal epithelium or kidney tissue

The diagnosis of CHV infection is most easily established in cases of neonatal death because the clinical signs and postmortem lesions are very characteristic. Grossly, the lesions consist of multifocal, diffuse hemorrhages and gray discoloration of parenchymal organs, especially the kidney, liver, and lungs. Microscopically, multifocal, necrotizing lesions are found. The virus can be isolated from many organs, especially the adrenals, lung, liver, kidneys, and spleen. In cases of neonatal death, chilled (not frozen) samples from the liver, kidney, and spleen should be submitted for virus isolation and formalin fixed for histopathologic examination. The whole abortus or placenta can be submitted chilled for virus isolation. Although FHV infection causes

abortion in pregnant cats, the virus is usually not recoverable from aborted material. Intranuclear inclusions are found in histologic specimens from the uterus, placenta, and aborted fetus of infected queens.

Herpes virus infection is prevented and controlled by changing management practices. Crowded conditions should be eliminated. Herpes viruses are very labile, and commonly available disinfectants are effective in destroying them. Sanitation and hygiene should be improved. Animals should be segregated according to life stages. Pregnant females and neonates should be isolated from all other colony members to prevent exposure to asymptomatic carriers. Although a bitch infected late in pregnancy is likely to suffer neonatal losses, she is also likely to acquire some immunity, which will protect her subsequent litters. For that reason, neonatal CHV usually is not a recurrent problem in an individual bitch. Neonatal CHV may remain a colony problem, however, unless management practices are changed. Vaccines are available.

# OTHER CAUSES OF PREGNANCY LOSS

Viral agents are the most commonly reported infectious cause of abortion in queens. Calici virus is one of the most important. In addition to calici and herpes viruses, parvo virus (panleukopenia), feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis have been implicated as causes of abortion in cats. Canine distemper is reported to cause bitches to abort.

Apparent luteal insufficiency is discussed as a cause of resorption and abortion, but it is rarely documented in bitches or queens. Determination of serial serum progesterone concentrations would be the first step in documenting this problem. Certain drugs that may be used to treat or prevent maternal illness are also known to be toxic to pregnant females, to be teratogenic, to cause fetal death, or to cause abortion (Box 58-3). Nutritional imbalances can cause pregnancy loss. This can be prevented by feeding highquality commercial pet foods that are labeled for reproduction and lactation or labeled for use in all life stages.

Fetal anomalies and chromosomal aberrations are reported to be a major cause of spontaneous abortion in women. Anatomic abnormalities are found in 20% of kittens that are stillborn or that die during the first 3 days of life. Most congenital fetal anomalies have no identifiable cause. Some are known to be heritable. Some are caused by environmental factors, such as exposure to teratogens. Chromosomal anomalies have been poorly investigated as a cause of spontaneous abortion in domestic animals, but they have been identified in some stillborn kittens and puppies. When normal-appearing, full-term puppies or kittens are stillborn, the most likely cause is fetal distress during parturition. Subsequent pregnancies and labor should be monitored more closely for signs of fetal stress.

# **Diagnosis of Resorption and Abortion**

The diagnostic efforts are directed toward finding the cause of resorption and abortion so that (1) the dam and any



BOX 58-3

Examples of Drugs with Probable or Known Risk to Pregnancy in Dogs and Cats

#### Hormones

Glucocorticoids

Prostaglandins

Prolactin inhibitors

Androgens

Estrogens

Excessive thyroid hormones

#### **Antimicrobials**

Aminoglycosides

Amphotericin B

Chloramphenicol

Ciprofloxacin

Doxycycline

Enrofloxacin

Griseofulvin

Metronidazole

Oxytetracycline

Tetracycline

#### **Nonsteroidal Antiinflammatory Drugs**

Anticonvulsants

**Anticancer Drugs** 

#### Anesthetics/Preanesthetics

Barbiturates

Diazepam

Halothane

Methoxyflurane

# Antiparasitic Drugs

Amitraz

Levamisole

Thiacetarsamide

Trichlorfon

#### Miscellaneous

Captopril

**Dantrolene** 

Dimethylsulfoxide (DMSO)

Diphenoxylate

**Excessive** vitamins

Isoproterenol

Loperamide

Methocarbamol

Methscopolamine

Mitotane (o,'p'-DDD)

Nitroglycerin

Nitroprusside

Propranolol

Thiazide diuretics

remaining viable fetuses can be treated properly, (2) the problem can be avoided during the subsequent pregnancies of this particular female, and (3) the rest of the colony can be protected from similar occurrences. The diagnostic approach should begin with a thorough history taking that includes such factors as changes in the bitch's or queen's environment, the recent addition of new animals to the house or kennel, the vaccination status of the animal, current drug therapy being given, and dietary supplements being administered. This should provide clues to possible exposure to infectious agents and teratogens. Many of the potential causes of fetal resorption-abortion can be excluded or identified during a careful history taking.

The dam should be thoroughly examined for signs of illness and the presence of remaining fetuses. Bitches and queens may abort part of a litter and carry the rest to term. Diagnostic imaging should be performed to determine the status of the uterine contents. Radiographs are most useful for identifying and counting fetal skeletons. Ultrasound is most helpful in assessing the viability of any remaining fetuses and assessing the character of other uterine contents, such as fluid or retained placentas. The metabolic status of the dam or queen should be determined with appropriate laboratory tests, such as a CBC, a serum biochemistry panel, and urinalysis. A sample of the uterine discharge obtained from the anterior vagina should be submitted for bacterial culture and antibiotic sensitivity testing. Appropriate serologic tests (e.g., Brucella titer, feline calicivirus) should also be performed on the dam. The abortus and placenta should be submitted for gross, microscopic, and microbiologic examinations. This complete postmortem examination of the abortus is the single most helpful procedure when attempting to identify the causes of abortion.

Hereditary causes of fetal anomalies may be difficult to prove. Knowledge of the hereditary defects common to the breed is an important aspect of such investigations. The breeding records of related animals should be scrutinized to determine whether there have been similar occurrences. If any are found, hereditary causes become more likely. If birth defects occur in subsequent litters from the same dam and sire, both should be eliminated from the breeding program. If hereditary causes and environmental causes (i.e., exposure to teratogens) can be ruled out, the dam and sire can reasonably be bred again because most birth defects have no identifiable cause, occur sporadically as isolated events, and do not recur in subsequent pregnancies.

#### **Treatment**

Therapy for the aborting female is supportive and symptomatic unless a cause can be found. If viable fetuses remain, the pregnancy can be allowed to continue. If not, any remaining contents of the uterus should be removed by ovariohysterectomy or through the administration of ecbolic agents as described for the treatment of pyometra in Chapter 57. Antibiotics should be administered as soon as appropriate specimens for microbiologic and serologic studies have been obtained. In many bitches and queens fetal resorption-

abortion is an isolated event with no identifiable cause or treatment. Subsequent breedings are often uneventful.

The next pregnancy should be monitored closely with ultrasonography, beginning about day 10 for queens and about day 15 for bitches, to differentiate failure to conceive from early embryonic death and to recognize impending resorption by the delay in development of specific structures or a slow fetal growth rate. Fetal death will be recognized by lack of cardiac activity and fetal movement. The status of the CL (possible luteal insufficiency) and the placenta can be monitored with serial serum concentrations of progesterone and relaxin, respectively. To evaluate the possibility of premature labor, uterine activity can also be monitored (WhelpWise.com).

# OTHER PREGNANCY DISORDERS

With the availability of uterine monitoring, premature labor has now been identified in bitches. Its prevalence and causes are unknown. At this time, treatment recommendations follow those for women but experience is limited so far. Uterine rupture is uncommon in the dog and cat. It occurs during or after labor. Typically, the animal presents with an acutely painful abdomen. Other causes of acute abdominal pain are excluded by diagnostic imaging and biochemical evaluation. The diagnosis is confirmed by exploratory surgery. Treatment is ovariohysterectomy. Ectopic pregnancy rarely occurs in bitches and queens. The clinical signs are usually nonspecific abdominal discomfort or the finding of an abdominal mass. Diagnostic imaging usually reveals a mummified fetus (Fig. 56-9). Treatment is surgical excision. The gravid uterus occasionally is incarcerated in an abdominal wall hernia. Presumably, this is the result of blunt abdominal trauma. Severe electrolyte and glucose abnormalities have been reported in the occasional pregnant bitch and queen and in association with retained fetuses. Treatment is aggressive fluid therapy appropriate to the specific metabolic derangement. Some pregnant animals responded well enough to carry their litters to term. Others were spayed as a part of the treatment plan.

# **MISMATING (ABORTIFACIENTS)**

Queens and bitches may occasionally mate at an undesirable time or with an undesirable male. The dilemma is then whether and how to prevent the birth of unwanted puppies or kittens without offending the moral sensibilities of the owner and veterinarian or threatening the health of the dam and her future reproductive capabilities. If continued reproductive function is not important, ovariohysterectomy can be performed when the female goes out of heat. Ovariohysterectomy should be performed during the first 3 to 4 weeks of diestrus because doing so is less likely to cause galactorrhea than when performed after 30 days in diestrus.

If continued reproduction is important, a question is whether to intervene immediately or wait until pregnancy is confirmed, at about 25 days. A single mating does not always result in pregnancy. As many as 26% to 62% of bitches examined 25 to 40 days after a misalliance are found to be not pregnant. Therefore an option is to do nothing until pregnancy has been confirmed. The risk that this misalliance might result in conception could be assessed by vaginal cytology and serum progesterone concentration, although this is not commonly done. Spermatozoa may sometimes be found on vaginal cytology during the first 24 hours after breeding. Their absence, however, does not preclude the possibility that insemination has occurred. Finding basal serum concentrations of progesterone (<1 ng/ml) indicates that ovulation has not yet occurred, whereas finding progesterone concentrations around 10 ng/ml to 20 ng/ml indicates optimal fertility. Some owners may elect to intervene early, especially if the risk of conception seems high, rather than to wait until pregnancy is confirmed. At this time, our recommendation is to wait until pregnancy is confirmed rather than to treat unnecessarily because the abortifacients currently available in the United States have side effects.

As with the treatment of pyometra, a variety of luteolytic and uterotonic drugs can be used to induce abortion (Box 58-4). Luteolysis is important to stop continued progesterone production, which is necessary to maintain the endometrium for implantation, maintain the health of the placenta, and suppress myometrial activity. Myometrial contractions are necessary to expel the uterine contents. Dopamine agonists such as bromocriptine and cabergoline suppress luteal activity by suppressing prolactin, which is luteotropic in bitches. Prostaglandins, such as prostaglandin  $F_{2\alpha}$  and clo-



# Therapeutic Options for Canine Misalliance

Do nothing

Ovariohysterectomy (may cause galactorrhea)

Estrogen not recommended

Natural PGF<sub>2\alpha</sub> (Lutalyse):

0.1-0.25 mg/kg SC q8-12h 30 to 35 days after breeding or

0.15-0.25 mg/kg SC q12h for 4 days; begin day 5-11 of cytologic diestrus

Cats: after day 45, 0.25 mg/kg SC q24h or q12h for 5 days (may produce side effects)

Cabergoline: 5 µg/kg PO q24h for 5 days, week 7 or

Cloprostenol (Estrumate): from day 25 after LH surge
1 μg/kg SC q48h, plus cabergoline 5 μg/kg PO q24h,
to effect or

 $2.5 \, \mu g/kg$  SC once, plus cabergoline  $5 \, \mu g/kg$  PO q24h for 10 days

Aglepristone: two SC doses (10 mg/kg) 24 hours apart, day 0-45 after breeding

prostenol, cause luteolysis via apoptosis, and they also cause myometrial contractions. Competitive antagonists of the progesterone receptor, such as aglepristone, block the effects of progesterone on the uterus and cervix. All these drugs will cause the next interestrous interval to be shortened by 1 to 3 months. None of these drugs is labeled for use in dogs and cats in the United States, although veterinary preparations are available in many other countries. Women who might be pregnant should handle all these drugs with great care.

#### **ESTROGENS**

Estrogens cause delayed transport of the embryo through the uterine tube, which results in degeneration of the embryo. Although some estrogens are effective in preventing pregnancy, their use has been discouraged for the following reasons. Pyometra develops in some bitches given estrogen during diestrus. Estrogens can prolong the duration of behavioral estrus, predispose to cystic ovarian follicle formation, and cause aplastic anemia. These effects are dose dependent, but aplastic anemia develops in some bitches given the recommended dose. If estrogens are used, they should not be administered during diestrus, as determined by vaginal cytologic findings. Estradiol cypionate (ECP) is no longer approved for use in dogs in the United States. Estradiol benzoate, 0.2 mg/kg, given intramuscularly 2 days after mating, prevented pregnancy in all 10 bitches in which it was administered. Animals were monitored for 75 days posttreatment. No uterine abnormalities were detected on ultrasound examination performed every 5 days, and no changes were found on CBCs performed every 12 days.

# **PROSTAGLANDINS**

After pregnancy has been confirmed, prostaglandins are administered until abortion is complete. This is determined by abdominal ultrasound. If treatment is stopped before the entire litter is aborted, the remaining fetuses may be carried to term. Prostaglandin  $F_{2\alpha}$  (0.1 to 0.25 mg/kg; Lutalyse, Pfizer) is administered to bitches subcutaneously, q12h to q8h daily, beginning 30 to 35 days after breeding and continuing until abortion is complete, which is accomplished in 3 to 9 days. In queens 0.2 mg/kg of natural PGF<sub>2 $\alpha$ </sub> administed subcutaneously, q12h for 5 days, beginning about day 45 of gestation, was effective in three of four queens. However, treatment was discontinued after 5 days because of side effects. Side effects include panting, salivation, emesis, defecation, urination, mydriasis, and nesting behavior. Intensive grooming behavior and vocalization may also be seen in the queen. Adverse reactions usually develop within 5 minutes of  $PGF_{2\alpha}$  administration and last for 30 to 60 minutes. The severity of reactions is directly related to the dose administered and inversely related to the number of days of therapy. Adverse reactions tend to become milder with subsequent injections.

Fewer side effects are reported for cloprostenol (Estrumate<sup>®</sup>, Schering-Plough); however, gastrointestinal signs still occur in 30% to 54% of bitches given the drug.

In bitches cloprostenol, 1.0 microgram/kg, is administered subcutaneously, q48h, beginning 25 to 42 days after breeding and continuing until abortion is complete. This occurs in 1.5 to 10 days, with a mean of 4 days. In those treated early, pregnancy ends by resorption. In those treated later, abortion occurs. A mucoid sanguineous discharge is present for 3 to 10 days. Given the fewer side effects and fewer injections, cloprostenol may be a better choice than prostaglandin  $F_{2\alpha}$ .

The dopamine antagonist cabergoline may be used with cloprostenol at a dose of 5 µg/kg orally, q24h. Gastrointestinal signs are the most common side effect of cabergoline (Galastop®, Ceva Vetem; Dostinex®, Pfizer).

Another protocol involves administration of one of the prostaglandins to bitches early in diestrus, before it is known if pregnancy exists. The advantage of early treatment is that fetuses are resorbed rather than expelled. Postabortion sequelae such as vulvar discharge are also minimal compared with those in bitches treated after day 30 to 35 of gestation. The disadvantage is that some animals will be subjected needlessly to treatment side effects. The protocol is begun no sooner than day 5 of cytologic diestrus, up to day 15 of diestrus. PGF<sub>2α</sub> is administered q12h for 4 days, or cloprostenol is administered q12h for 5 days using the dosages previously discussed. The serum progesterone concentrations are determined at the end of treatment. Fetal death is likely if the serum progesterone concentration declines and remains below 2 ng/ml (approximately 6.4 nmol/L) for 48 hours. If the progesterone concentration is greater than 2 ng/ ml after treatment, luteolysis is not complete, in which case the pregnancy status should be assessed with ultrasonography or a second course of treatment should be administered. In either case reevaluation by ultrasound and/or progesterone determination at 20 days is recommended. When treatment is stopped without confirming the success of pregnancy termination, about 15% of treated bitches will carry their litters to term.

# **ALTERNATIVE TREATMENTS**

Cabergoline can be used as a single agent. When given after 7 weeks of gestation in bitches, cabergoline (5  $\mu$ g/kg, administered orally q24h for 5 days) causes abortion in 3 to 5 days with few side effects. Unfortunately, at this late stage of gestation recognizable fetal parts or live fetuses that die shortly thereafter may be passed. Parturition (i.e., full-term pregnancy) was prevented in 12 of 14 feral cats given cabergoline in their feed at a dose of either 25  $\mu$ g/day for 5 days or 50  $\mu$ g/day for 3 days.

A single course of aglepristone (Alizine®, Virbac, Carros, France) has an efficacy of 97% in bitches and 87% in queens, when administered at any time from the day of copulation to day 45. The dose for bitches is 10 mg/kg, given subcutaneously twice, 24 hours apart. The dose for cats is 10 or 15 mg/kg, given subcutaneously twice, 24 hours apart. The only side effect reported for aglepristone is transient pain or swelling at the injection site. Massaging the injection site to help disperse the drug can minimize this reaction. Resorption or

abortion occurs 1 to 7 days after treatment. On the day of fetal expulsion animals may be somewhat lethargic. The postabortion discharge typically lasts for 1 to 5 days. The animals in which pregnancy is not terminated may deliver a live litter at term, give birth to dead fetuses, or retain them. For this reason the effect of treatment should be determined by posttreatment ultrasound. If fetuses remain, another dose of aglepristone may be tried or prostaglandins can be administered. Given its efficacy and safety, aglepristone is a good choice for early and midgestation pregnancy termination in dogs and cats.

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# CHAPTER Postpartum and Mammary Disorders

# CHAPTER OUTLINE

#### POSTPARTUM DISORDERS

Metritis

Puerperal Hypocalcemia (Puerperal Tetany, Eclampsia) Subinvolution of Placental Sites

# MAMMARY GLAND DISORDERS

Mastitis

Galactostasis

Agalactia

Galactorrhea

Feline Mammary Hyperplasia and Hypertrophy

Mammary Neoplasia

# **POSTPARTUM DISORDERS**

#### **METRITIS**

Metritis is an acute postpartum bacterial infection of the uterus. It also may occur after abortion, dystocia, retention of placental or fetal tissues, obstetric procedures, or normal parturition. Bacteria that ascend from the vagina are the cause. Affected animals are febrile and have a fetid, septic uterine discharge. Dehydration, septicemia, endotoxemia, shock, or a combination of these can occur. One of the earliest signs of maternal illness is unthrifty, crying neonates that are being neglected by the dam. Metritis and mastitis are the two most common causes of fever and neonatal neglect in the postpartum bitch.

# Diagnosis

The diagnosis is based primarily on the historical and physical findings. Diagnostic imaging should be done to evaluate the uterine contents (e.g., fetal remnants) and assess the integrity of the uterus. Bacterial culture and sensitivity testing of the uterine discharge should be performed. The overall health of the dam can be further assessed with a complete blood count (CBC) and biochemical panel if indicated. The septic nature of the discharge can be confirmed

by cytologic examination. The uterine source of the exudate can be confirmed with endoscopic studies, but this is usually not necessary.

#### **Treatment**

For the sake of neonatal survival, metritis should be treated promptly and aggressively to minimize the hospital stay. Infected uterine contents can be removed surgically by ovariohysterectomy or medically with the administration of ecbolic agents. The decision to manage metritis medically or surgically is determined by the health of the bitch or queen, the integrity of the uterus, and the owner's desire for the animal to be able to reproduce in the future. Regardless of the approach taken, intravenous (IV) fluid therapy should be aggressive to correct existing deficits, maintain tissue perfusion, and provide for the additional demands of lactation, which are substantial. The antibiotic should be chosen on the basis of the results of a culture of the uterine exudate obtained from the anterior vagina. It is assumed that the antibiotic will reach the neonates through the milk; therefore the potential for deleterious effects on the neonates should be considered (Box 59-1). When future reproductive function is not important, in cases of potential uterine rupture, and in situations in which the dam is critically ill, ovariohysterectomy should be performed.

Medical, rather than surgical, management of metritis is appropriate for animals that are in stable condition. Drugs that cause myometrial contractions, such as the prostaglandin cloprostenol, are used to promote the evacuation of infected uterine contents, as described for the treatment of pyometra in Chapter 57. The luteolytic aspects of the drugs are not needed for the treatment of postpartum metritis because the corpora lutea (CLs) are no longer present, but they may be helpful in cases of postabortion metritis in which serum progesterone may still be high. Treatment should continue until the uterus is empty, as determined by ultrasound. This usually takes several days. Aglepristone (Alizine®, Virbac), which blocks the progesterone receptor, has also been successfully used to treat metritis in bitches. The dose of aglepristone is 10 mg/kg, administered subcutaneously once daily on days 1, 2, and 8.



#### **Antimicrobial Therapy for Neonates**

# **Drugs with Known Safety**

Amoxicillin-clavulanate Amoxicillin Cephalosporins Erythromycin Penicillins Tylosin

#### Safety not Established

Clindamycin Lincomycin

#### Drugs Known to Cause Undesirable Effects

Aminoglycosides Chloramphenicol Ciprofloxacin Enrofloxacin Nalidixic acid Nitrofurantoin Norfloxacin Polymyxin Sulfonamides Tetracyclines Trimethoprim

# PUERPERAL HYPOCALCEMIA (PUERPERAL TETANY, ECLAMPSIA)

Puerperal tetany is an acute, life-threatening hypocalcemia that occurs in the postpartum period. Clinical signs are a direct result of hypocalcemia and include muscle fasciculation and tetany but not true seizures. The cause of the hypocalcemia is usually undetermined, but it could result from such problems as maternal calcium loss to the fetal skeletons and to the milk, poor absorption of dietary calcium, and parathyroid gland atrophy caused by improper diet or dietary supplements. Clinical signs of puerperal hypocalcemia typically develop during peak lactation (i.e., 1 to 3 weeks postpartum) in small bitches that are nursing large litters. The dam is otherwise healthy, and the neonates are thriving. Puerperal hypocalcemia also can occur in cats, in any breed of dog, with any size litter, and at any time during lactation. Rarely, hypocalcemia occurs during late gestation in bitches and queens and may contribute to dystocia.

#### **Clinical Features**

The clinical signs are caused by hypocalcemia and include panting, trembling, muscle fasciculation, weakness, and ataxia. These early clinical signs quickly progress (e.g., within hours) to tetany with tonic-clonic spasms and opisthotonos. Heart rate, respiratory rate, and rectal temperature are increased, especially during tetany. Clinical signs are

rapidly progressive and may be fatal if the animal goes untreated.

# Diagnosis

Puerperal hypocalcemia is diagnosed on the basis of the typical clinical signs in a heavily lactating female. It can be confirmed by measuring the serum concentrations of calcium, which typically are below the reference range. Because the clinical signs in postpartum bitches are so suggestive, treatment is usually initiated before, or without, laboratory confirmation. Laboratory confirmation would be necessary in a prepartum animal. Although severe hypoglycemia could cause similar clinical signs, it is a rare postpartum disorder in the bitch or queen.

#### **Treatment**

Treatment consists of the slow IV administration of a 10% solution of calcium gluconate, to effect. The total dose is usually 3 to 20 ml, depending on the size of the bitch or queen. Because calcium is cardiotoxic, the animal's heart must be closely monitored for the development of dysrhythmias and bradycardia during treatment. Calcium administration must be stopped immediately if any cardiac abnormalities are detected. If additional calcium is still needed, it should be administered as soon as the cardiac rhythm has normalized, but the rate of administration should be much slower. The response to treatment is dramatic, and clinical signs resolve during IV calcium administration.

Puppies or kittens should then not be allowed to nurse for 12 to 24 hours. Oral calcium (gluconate, carbonate, or lactate), 1 to 3 g daily, should be administered for the duration of lactation. The dam's diet should also be adjusted to ad libitum feeding or at least feeding three times a day. The diet should be high-quality commercial food that is labeled as nutritionally complete, balanced, and appropriate for lactation. Some veterinarians also recommend that dams be given vitamin D supplementation, but this must be done with caution because hypercalcemia can occur in response to overzealous vitamin D supplementation. Usually, a balanced diet with additional oral calcium suffices to prevent hypocalcemia. If hypocalcemia recurs, the puppies should be weaned.

# **Prevention**

Several steps can be taken to prevent puerperal hypocalcemia in the bitch and queen. First, a high-quality, nutritionally balanced and complete diet should be fed to the bitch or queen during pregnancy and lactation. Second, oral calcium supplementation during gestation is contraindicated because it may worsen, rather than prevent, postpartum hypocalcemia. Finally, the bitch or queen should have access to food and water ad libitum during lactation. If necessary, the dam can be physically separated from the neonates for 30 to 60 minutes several times a day to encourage her to eat. Supplemental bottle-feeding of the litter with milk replacer early in lactation and with solid food after 3 to 4 weeks of age may be helpful, especially for large litters.

#### SUBINVOLUTION OF PLACENTAL SITES

In the bitch normal postpartum involution of the uterus occurs over 12 weeks. The placental sites and the entire endometrium slough. By the ninth week the uterine horns are uniformly contracted, and the surface sloughing is complete. Replacement of the endometrial lining continues until the twelfth postpartum week, at which time involution is complete. The sloughed material makes up the normal postpartum vulvar discharge known as *lochia*. Immediately after whelping, lochia contains large amounts of the placental blood heme pigment called *uteroverdin*. This makes the lochia dark green for the first few hours (<12 hours). Thereafter the lochia is reddish or red-brown and contains cellular debris and mucus. The volume of lochia diminishes quickly, and within a few weeks it is an intermittent (several times a day) spotting of reddish or red-brown mucoid material.

Subinvolution of placental sites (SIPS) results in persistent postpartum dripping of sangineous discharge for 12 or more weeks. SIPS is most common in primiparous bitches younger than 3 years of age, but it can occur in older multiparous animals as well. It has not been reported in cats. The cause is unknown.

# **Diagnosis**

Affected bitches are healthy and physically normal, except for a small amount of bloody vulvar discharge. The blood loss from SIPS is not severe. If the clinician is concerned, the CBC can be evaluated, keeping in mind the normal decline in the packed cell volume (PCV) that occurs during pregnancy. Vaginal cytology (see Chapter 56) can be used to differentiate the bleeding associated with SIPS from lochia and from the discharge associated with metritis. Cytologically, evidence of hemorrhage is found. Decidua-like multinucleated giant cells may also be seen. Ultrasound can be used to assess the degree of uterine involution. The diagnosis of SIPS usually is based on the historical, physical, and cytologic findings alone. It can be confirmed by histopathologic examination of the placental sites, but this is rarely necessary. Normally involuted placental sites and SIPS can be found in the same uterus.

Bitches with SIPS rarely require treatment. Recovery is spontaneous, and subsequent fertility is not affected. Ovariohysterectomy is curative. The administration of ergonovine maleate, oxytocin, or prostaglandin will cause uterine contraction and may diminish bleeding, but there is little published evidence that this hastens recovery from SIPS. Progestin therapy has also been suggested, but its undesirable effects on the endometrium outweigh any potential benefit in this situation. If anemia is severe enough to require treatment, a diagnosis other than SIPS should be considered.

# DISORDERS OF THE MAMMARY GLANDS

#### **MASTITIS**

Mastitis is a bacterial infection in one or more of the lactating mammary glands. It is a common postpartum disorder in bitches. It is rare in queens. Mastitis rarely occurs in bitches that are lactating because of false pregnancy. Whenever inflammation and/or abnormal secretions are present in nonlactating glands, mammary neoplasia should be strongly considered as the cause. The clinical signs of mastitis are variable in severity but include fever; anorexia; dehydration; and warm, firm, swollen, painful glands. Crying, unthrifty puppies may be what the owner notices first because bitches that are ill with mastitis may neglect them. In severe cases abscesses or gangrene of the glands can develop. Mastitis is the most common cause of postpartum fever. The diagnosis is made on the basis of these physical findings in a lactating female and on the septic appearance of the mammary secretions. Escherichia coli, staphylococci, and β-hemolytic streptococci are the organisms most frequently isolated.

The treatment of mastitis includes antibiotics, fluid therapy, and supportive care. It should be aggressive to ensure that the bitch can resume her maternal duties as soon as possible. Adequate water and caloric intake is crucial to ensure continued milk production. During lactation food and water needs are often double what they were during gestation. The additional fluid needs to support lactation must be taken into account when planning fluid therapy. Warm compresses applied to affected glands several times a day can reduce swelling and pain, and this should be included in the treatment of mastitis.

There are several factors to consider in the choice of antibiotics, including the susceptibility of the infecting organisms, the ability of the antibiotic to achieve high concentrations in milk, and the effects of the drug on the nursing neonate (see Box 59-1). Amoxicillin and cephalosporins can be used if the results of bacterial culture are not known because they are likely to achieve reasonable concentrations in the infected gland, they are likely to be effective against the most common organisms, and they are reasonably safe for neonates. Mammary abscesses and gangrene should be treated surgically.

It is recommended that pups continue nursing as long as the dam is willing and able to provide adequate nutrition. Monitoring the weight gain of the puppies, which should be about 10% per day, helps the clinican assess whether the puppies' needs are being met. The pups should also be watched closely for other signs of illness. If present, supplemental feeding or hand-rearing of the puppies should be considered.

#### **GALACTOSTASIS**

Galactostasis is the accumulation and stasis of milk within the mammary gland. This results in warm, firm, swollen, painful glands. Unlike mastitis, in galactostasis the mammary secretions are not infected and the dam is not ill. Milk is simply being produced faster than it can comfortably be stored. Galactostasis usually occurs at the time of weaning and occasionally at the time of peak lactation, when production transiently exceeds the needs of the neonates. Galactostasis may also occur with false pregnancy (see Chapter 58).

Treatment is not indicated for the transient galactostasis that occasionally occurs during the first 1 to 3 weeks of lac-

tation. If treatment is necessary for galactostasis that occurs at weaning, it is directed toward reducing milk production and relieving discomfort. Milk production diminishes as food and water intake is restricted. Therefore reducing the caloric intake to amounts appropriate to maintain ideal body weight and normal hydration during anestrus (i.e., neither pregnant nor lactating) is helpful in treating, as well as preventing, the galactostasis that occurs at weaning. Gradual, rather than abrupt, weaning is also helpful. Because massaging or expressing the mammary glands may stimulate prolactin release and promote continued lactation, these techniques are not recommended. Warm compresses may help relieve swelling and discomfort.

#### **AGALACTIA**

Agalactia is the absence of milk production or secretion. Normal milk production and secretion are dependent on many factors, including genetics, nutrition, psychological factors, and anatomic differences. Prolactin stimulates milk production. Oxytocin stimulates milk letdown. Primary agalactia refers to a situation in which the gland is incapable of producing milk or the ducts are incapable of flow. More commonly, the gland and ducts are normal but other factors have diminished the capacity for production or inhibited milk letdown. Animals that are in poor body condition may have difficulty establishing and maintaining lactation. Caloric and water needs during lactation are as much as double those needed during gestation. To ensure that the needs of both gestation and lactation are met, a high-energy diet, appropriate for reproduction and lactation, should be fed from the time of breeding onward. Unlike multiparous animals that may have colostrum that is easily expressed during the last week of gestation, primiparous animals may not produce colostrum at this time; however, colostrum is almost always present within 24 hours of parturition.

Anxiety will inhibit milk letdown. The nursing dam and her litter should be in a quiet location, with limited visitors, especially for the first several days. If necessary, sedation may be considered. Phenothiazines may increase prolactin secretion, which would be beneficial. Oxytocin, 0.5 to 2.0 U administered subcutaneously q2h, has also been suggested to promote milk letdown. It is available for this purpose in people in the form of a nasal spray. Puppies or kittens are returned to nurse 30 minutes after oxytocin is administered. Metoclopramide stimulates prolactin secretion and has been successfully used to enhance lactation. The dose is 0.1 to 0.2 mg/kg (administered orally or subcutaneously) q6-8h until lactation is adequate. The oral dose may be increased to 0.5 mg/kg q8h if needed. Treatment is usually needed for only a day or two. Meanwhile, nutritional and psychological factors must also be corrected.

# **GALACTORRHEA**

Galactorrhea refers to lactation that is not associated with pregnancy and parturition. It is the most common clinical manifestation of false pregnancy in the bitch. Galactorrhea of false pregnancy occurs at the end of diestrus, after the withdrawal of exogenous progestins, or after oophorectomy performed during diestrus. This galactorrhea is self-limiting and usually does not require treatment. See Chapter 58 for details of the condition.

# FELINE MAMMARY HYPERPLASIA AND HYPERTROPHY

Feline mammary hyperplasia (fibroepithelial hyperplasia, fibroadenoma, fibroadenomatosis) is characterized by the rapid, abnormal growth of mammary tissue. Hyperplasia of both epithelial and mesenchymal tissues is evident microscopically. It is most common in young, cycling queens that may or may not be pregnant (Fig. 59-1). It has also been observed in neutered male and neutered female cats that are receiving exogenous progestins. There is a strong temporal relationship between the onset of mammary hyperplasia and progesterone stimulation. Feline mammary hyperplasia is a benign condition, but its abnormal growth may mimic those of mammary neoplasia. Histologic evaluation of a biopsy specimen can be done if there is any doubt.

Treatment consists of removing the source of the progesterone. Although successful pregnancy and nursing of kittens were reported in one queen with mammary hyperplasia, ovariohysterectomy is usually recommended, irrespective of the pregnancy status. The surgery is often performed through a flank incision rather than through the usual midline approach, because of the massive size of the glands. The hyperplastic tissue resolves over several weeks following oophorectomy. The prognosis is excellent. In the unlikely event that there is no response to withdrawal of progestins or ovariohysterectomy, the progesterone receptor blocker aglepristone (Alizine®, Virbac), 20 mg/kg administered subcutaneously on one day or 10 mg/kg on two consecutive days once weekly, resolves the condition in 1 to 4 weeks. The only side effect is irritation at the injection site; however, aglepristone will cause abortion if the queen is pregnant. Mastectomy may be indicated if the abnormal mammary tissue has become necrotic.

#### MAMMARY DUCT ECTASIA

Mammary duct ectasia is a benign, sometimes painful condition in which the mammary collecting ducts are dilated by inspissated secretions. It occurs in neutered and intact bitches of any age, but the mean age at the time of diagnosis is 6 years. The clinical signs resemble those of mammary neoplasia. The cystic nature of the condition can often be appreciated on palpation. The inspissated material is yellow or bluish in color and is sometimes visible beneath the skin. Surgical excision is curative. The mass should be submitted for histopathologic evaluation because mammary neoplasia is the other likely differential diagnosis.

# MAMMARY NEOPLASIA

# Etiology

Mammary neoplasms account for about half of all tumors in bitches. Although they are less prevalent in queens,

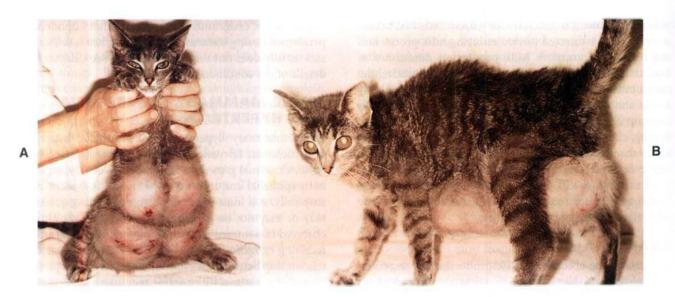


FIG 59-1 Mammary hyperplasia of 6 weeks' duration in a 5-month-old queen.

mammary neoplasms are still the third most common tumor type in cats. They primarily affect older animals, with a mean age of about 10 years. Most affected animals are intact females or females that have undergone oophorectomy after 1 or 2 years of age. Mammary tumors are rare in males and in young animals of either sex.

Early ovariohysterectomy is strongly protective against the development of mammary tumors. Bitches neutered before their first estrous cycle are at no greater risk for mammary tumors than are males. After 2.5 years of age or after the second estrous cycle, ovariohysterectomy is apparently no longer protective in bitches. Cats neutered before 1 year of age also have a significantly (86%) decreased risk of developing mammary carcinoma. The progestins used to suppress estrus promote hyperplastic and neoplastic changes in the feline and canine mammary glands. Benign mammary tumors are found in more than 70% of bitches receiving long-term progestin treatment. About half of mammary tumors in bitches are benign, whereas feline mammary tumors are almost always malignant.

#### **Clinical Features**

Mammary tumors are usually discrete, firm, and nodular. They may be found anywhere along the mammary chain. The size is extremely variable, ranging from a few millimeters to many centimeters in diameter. Multiple glands are involved more than half of the time. The tumors may adhere to the overlying skin but usually are not attached to the underlying body wall. Malignant tumors are more likely than benign tumors to be attached to the body wall and covered by ulcerated skin. About 25% of feline mammary tumors are covered by ulcerated skin. Abnormal secretions can often be expressed from the nipples of affected glands. Inflammatory carcinoma of a mammary gland may have a physical appearance similar to that of mastitis. However, inflammatory carcinoma is most likely to occur in geriatric animals, and there

is no association with lactation. The regional lymph nodes (axillary or inguinal) may be enlarged if metastasis has occurred. The remainder of the physical examination findings are often unremarkable. There may be evidence of tumor cachexia in animals with advanced neoplasia.

# **Diagnosis**

Mammary neoplasia is the most likely cause of any kind of nodule in the mammary gland of an older female. Excisional biopsy is the method of choice to confirm the diagnosis. Cytologic examination of specimens obtained by fine-needle aspiration often yields equivocal results. Before excisional biopsy is performed, radiographs of the thorax should be evaluated for evidence of pulmonary metastasis. If evidence of pulmonary metastasis is found, a grave prognosis is justified, even in the absence of histologic confirmation of mammary neoplasia. Malignant mammary tumors frequently metastasize to the regional lymph nodes and to the lungs. Less commonly, hepatic metastasis occurs. Metastasis to distant sites can also occur, but this rarely happens in the absence of local lymph node or pulmonary involvement. Diagnostic imaging and careful palpation are used to evaluate the tumor burden. The animal's overall health is assessed with a CBC, biochemical panel, and urinalysis.

## **Prognosis**

Approximately half of the mammary tumors in bitches are benign. Some of these benign tumors show evidence of cellular atypia within the parenchyma and are considered precancerous. Precancerous changes in bitches are associated with a ninefold increase in the risk of mammary adenocarcinoma developing at a later date. Animals with nodules of normal cellular characteristics are at no greater risk than animals with no previous mammary nodules. In contrast, benign mammary tumors are rare in cats. More than 80% of feline mammary tumors are classified as adenocarcinomas.

Adenocarcinoma is the most common malignant mammary tumor in bitches and queens. If the neoplastic cells are confined to the duct epithelium (carcinoma in situ), the prognosis after surgery is good. The prognosis is somewhat worse if neoplastic cells are found beyond the boundary of the duct system but not in blood or lymphatic vessels. The prognosis is worse if neoplastic cells are found in blood or lymphatic vessels. If neoplastic cells are found in the regional lymph nodes, the disease-free interval after surgery is significantly shortened. Nuclear differentiation affects the recurrence rates, even within the same stage of invasion. The recurrence rate 2 years after mastectomy in bitches with poorly differentiated (i.e., anaplastic) tumors is 90% versus rates of 68% and 24% in animals with moderately differentiated and well-differentiated tumors, respectively.

In queens mammary tumors are almost exclusively carcinomas. In bitches other malignant tumors of the mammary gland, such as inflammatory carcinoma, sarcomas, and carcinosarcomas, are occasionally found, but they are much less common than are adenocarcinomas. Inflammatory carcinoma is a fulminant malignant disease associated with a grave prognosis in bitches and queens.

#### **Treatment**

The treatment of mammary neoplasia is surgical excision of all abnormal tissue. Controversy persists as to the preferred surgical technique: nodule excision, simple mastectomy, or radical mastectomy. If nodulectomy is chosen, apparently normal surrounding tissue should always be included and submitted for histopathologic evaluation for evidence of tumor invasion. If there is evidence of extension beyond the nodule, mastectomy should be performed. There is no difference in the survival times after simple versus radical mastectomy in bitches and queens; however, the disease-free interval may be longer in cats that have undergone radical mastectomies. Excised mammary tumors should always be submitted for histopathologic examination because the tumor type determines the prognosis. The prognosis for inflammatory carcinoma is grave.

Because the surgical excision of malignant mammary tumors is not curative, the effectiveness of adjunct therapies has been investigated. There is no doubt that estrogen and progesterone play a role in mammary neoplasia. Mammary tumors express estrogen receptors or progesterone receptors (or both), which explains why some mammary masses appear to be hormone sensitive and others do not. The effects on survival of endogenous and exogenous hormones

continues to be of interest. To fully assess the therapeutic benefits of hormonal manipulation, the clinician must know the estrogen- and progesterone-receptor status of the tumors. In many veterinary studies that has not been the case.

Ovariohysterectomy performed at the time of mastectomy has no effect on 2-year survival rates in bitches. There also appear to be no differences in survival among bitches that undergo ovariohysterectomy before mastectomy, bitches that undergo ovariohysterectomy at the time of mastectomy, and bitches that undergo mastectomy alone, although data are conflicting. Tamoxifen competitively binds estrogen receptors with a combined antagonist-agonist effect. Its antiestrogenic effects are helpful in the treatment of mammary neoplasia in women. Tamoxifen has primarily estrogenic effects in dogs. In a study of the use of tamoxifen as adjunct therapy for canine mammary neoplasia, no beneficial antitumor effects were proved but 56% of the treated dogs showed adverse estrogenic effects. Although at present there is little published evidence of beneficial effects of chemotherapy as an adjunct to the surgical treatment of mammary tumors in bitches and queens, clinical investigations continue.

# **Suggested Readings**

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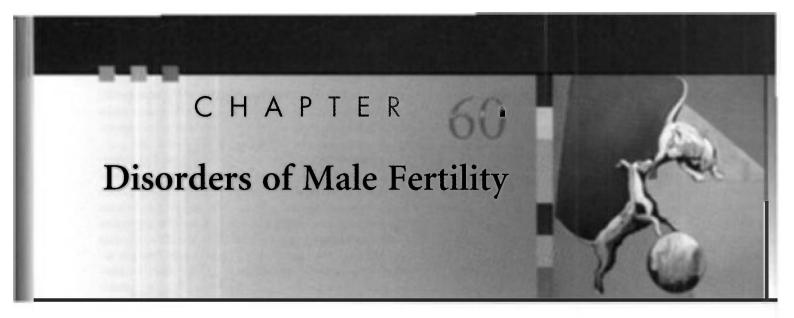
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# CHAPTER OUTLINE

NORMAL SEXUAL DEVELOPMENT AND BEHAVIOR

Development

Breeding Behavior

DIAGNOSTIC TECHNIQUES TO ASSESS

REPRODUCTIVE FUNCTION

Semen Collection and Evaluation

Bacterial Culture of Semen

Diagnostic Imaging

Hormonal Evaluation

Testicular Aspiration and Biopsy

DIAGNOSTIC APPROACH TO INFERTILITY

OLIGOZOOSPERMIA AND AZOOSPERMIA

CONGENITAL INFERTILITY

**ACQUIRED INFERTILITY** 

# NORMAL SEXUAL DEVELOPMENT AND BEHAVIOR

#### **DEVELOPMENT**

Sexual differentiation into a male or female has three components: chromosomal, gonadal, and phenotypic sex. The major genetic components that direct the development of a male are located on the short arm of the Y chromosome in the sex determining region, or Sry gene. Together with certain factors elsewhere on the sex chromosomes and on some autosomes, the Sry gene directs the development of the sexually indifferent fetal gonads into testes. Testicular differentiation is observed in the canine fetus at day 36 of gestation. The many hormones produced by the fetal testis cause continued sexual differentiation into the male phenotype. In the absence of these influences, the phenotype will become female. Fetal Sertoli cells produce Müllerian inhibiting substance, which causes regression of the Müllerian ducts that would otherwise have developed into the oviduct, uterus, and cranial vagina. Müllerian duct regression is complete by day 46 of gestation in dogs. Fetal Leydig cells produce testosterone, which causes the Wolffian ducts to develop into the ductuli deferentes and epididymes. Dihydrotestosterone, a metabolite of testosterone, causes the urogenital sinus, the genital tubercle, and the genital swelling to differentiate into the urethra and prostate, penis, and scrotum, respectively. The male external genitalia can be recognized by ultrasound between gestation days 38 to 43 in the feline fetus (Zambelli et al., 2006a). Factors produced by the fetal testis also cause the testis to descend from its fetal position near the caudal pole of the kidney, through the inguinal canal, into the scrotum. Normal testicular descent is a prenatal event in cats and is normally complete by 10 to 42 days of age in dogs. Although later descent is possible, a diagnosis of cryptorchidism should be considered if the testes are not palpable within the scrotum by 8 to 10 weeks of age.

The Leydig (interstitial) cells are stimulated by luteinizing hormone (LH) to produce testosterone and, in much lesser amounts, estradiol. In addition to the development of the ductus deferens and epididymis, testosterone initiates and maintains all aspects of spermatogenesis; supports libido; and, via negative feedback, regulates hypothalamic secretion of gonadotropin releasing hormone (GnRH) and pituitary secretion of LH and follicle-stimulating hormone (FSH). Testosterone is also the prohormone for dihydrotestosterone (DHT) and estradiol, which are formed in the testis and also in peripheral tissues, by the action of the enzymes  $5\alpha$ reductase and aromatase, respectively. DHT promotes the maturation of the prostate and the external genitalia and the development of the secondary sexual characteristics at puberty (see Fig 56-4). Only a small amount of estradiol is secreted by the testes. Most of the circulating estradiol in adult males is formed in the extragonadal tissues by the aromatization of circulating testosterone.

The Sertoli cells and spermatogonia (germ cells) are located along the basement membrane of the seminiferous tubules. Cytoplasmic processes from Sertoli cells extend from the lamina propria of the seminiferous tubules to the tubular lumen and surround the developing germ cells. Sertoli cells are regulated by FSH and testosterone to produce several substances that are necessary for spermatogenesis and normal spermatid maturation. In fact, spermatogenesis is regulated via the effects of FSH on Sertoli cells, not by

direct effects of FSH on germ cells. Specific functions of Sertoli cells vary according to the developmental stage of the germ cells they surround. These may also vary depending on the species of animal.

Sertoli cells convert testosterone, produced by the Leydig cells, to estradiol. This is especially apparent in prepubertal animals. Most of the testicular estradiol in adults appears to originate from Leydig cells. The role of estradiol in male reproduction is unclear. Along with testosterone, it is involved in the regulation of gonadotropin secretion. In some instances, estrogens augment the effects of androgens, such as in the canine prostate, where estradiol regulates the number of DHT receptors. In the mammary gland estrogens seem to have antiandrogenic effects. Sertoli cells also produce a substance known as androgen-binding protein, which is thought to moderate the effects of testosterone. It may also be involved in the transport of testosterone within the testis and epididymis. Sertoli cells also produce the hormones inhibin and activin. Inhibin causes a decrease in FSH secretion by the pituitary. Activin has the opposite effect on FSH secretion.

Spermatogenesis refers to the maintenance of spermatogonia and the differentiation of spermatogonia into spermatozoa within the seminiferous tubules. Both proliferating and noncommitted spermatogonia are located nearest the tubular basement membrane. As the germ cells mature into spermatocytes and eventually spermatids, they move toward the tubular lumen, such that the most differentiated cells are nearest the lumen. Eight to 10 stages of sperm development, or cellular associations, have been identified in dogs. They represent maturation of spermatogonia, then several stages of maturing spermatocytes, and finally several stages of maturing spermatids. A cross-section of any given normal seminiferous tubule contains all stages of the developing spermatozoa.

In addition to the proliferating spermatogonia, there is a population of noncommitted spermatogonia that are called  $A_0$ -spermatogonia. These spermatogonia remain in reserve and, unlike proliferating spermatogonia, are quite resistant to damage by toxins and radiation. The recovery of spermatogenesis that occurs after testicular injury results from the repopulation of the germinal epithelium by the progeny of the A<sub>0</sub>-spermatogonia. In dogs approximately 62 days elapse from the time A<sub>0</sub>-spermatogonia begin to differentiate into mature spermatogonia until the time mature spermatozoa are released into the tubular lumen. It then takes approximately 14 days for spermatozoa to become fully mature and motile in the epididymis. Frequent ejaculation does not influence daily sperm production in the testes, but it does diminish the number of sperm ejaculated by depleting the extragonadal reserves from the epididymis and ductus deferens.

Sexual maturity and physical maturity are closely related. Puberty occurs around 9 to 10 months of age in tomcats. The same is generally true for dogs, but the large and giant breeds mature more slowly. The onset of puberty is signaled by the development of masculine physical characteristics, such as heavier muscling and thicker skin on the jowls, and

sexual behavior, such as territorial urine marking and mounting of other colony members. Semen quality and serum concentrations of testosterone gradually approach those of mature males, although prepubescent males may be fertile. Semen quality and libido tend to decline with advancing age, especially in geriatric males. Although males are fertile long past 6 years of age, they often are less active in breeding programs. This is primarily because they are replaced by younger males with similar or preferred phenotypic and genotypic qualities. Because other health problems often develop in older animals, their physical ability to mate may decline. Undesirable behavior is cited as a common reason for retiring older tomcats from breeding colonies.

#### **BREEDING BEHAVIOR**

Much of normal breeding behavior is learned by dogs and cats. Consequently, early breeding experiences help determine a male's future success as a stud. There is usually one dominant male in any specific territory. Even if all males are given equal opportunity, the dominant male will do most of the breedings. Establishing dominance and territory is usually a prerequisite to mating; therefore the standard practice is to bring the female to the male. Because successful studs must be physically, sexually, and socially mature, it is usually recommended that males not enter a breeding program until they are at least 12 months old, even though puberty may have occurred months earlier. Dogs that are used in an artificial insemination program may become so accustomed to semen collection that they are no longer interested in natural service.

Ideally, a sexually inexperienced male should first be exposed to a docile, experienced female in his own territory. Virgin males usually make many unsuccessful attempts to mount before achieving intromission. This first encounter should be short and well supervised so that the male does not become frustrated or exhausted by his unsuccessful attempts to copulate or, worse, become intimidated or actually injured by an aggressive female. The tomcat typically grasps the queen's neck near her shoulders and straddles her with his front feet. The neck grasp is thought to be necessary to restrain the female and to properly position both animals' rear quarters to allow intromission to occur. The rear quarters are then straddled, and intromission occurs (Fig. 60-1).



FIG 60-1 Feline breeding behavior.

To insure adequate copulatory stimulation to induce ovulation in the queen, three breedings per day for the first 3 days of estrus are recommended (see Chapter 56). When semen is collected from cats three times per week, the volume and number of sperm are fairly constant from collection to collection. When semen is collected daily, by the fourth day the volume and number of sperm drop to less than half of that on the first day and then remain fairly constant at 14 to 45 million sperm per ejaculate. Libido and sperm motility and morphology did not change with frequent collection, other than an increase in the number of immature spermatozoa (Zambelli, 2006b).

Because the canine os penis maintains rigidity, intromission can and does occur before the penis is actually erect. During erection the bulbus glandis of the canine penis swells twofold to threefold, filling the vestibule and preventing separation of the breeding pair. Ejaculation of the first two seminal fractions begins shortly after intromission, during the rapid pelvic thrusting. Soon after its pelvic thrusting subsides, the dog dismounts and faces away from the bitch, but the erect penis, having turned 180 degrees in a horizontal plane, remains in the bitch. This is known as the postcoital lock or tie (see Fig. 56-2). Ejaculation, primarily of the third fraction, which consists of prostatic fluid, continues during the tie. The tie persists until the dog's erection subsides 15 to 30 minutes or more later. If the dog's penis is erect before intromission, the size of the bulbus glandis prevents complete intromission and a tie will not occur when the dog dismounts. Some dog owners refer to this as an outside tie. In this situation the entire ejaculate may not have been deposited in the bitch.

Two breedings during the fertile period are recommended for dogs because doing so has been shown to increase both whelping rates and litter size. When breeding is performed at the most optimal time during the fertile period, whelping rates are not significantly higher with two breedings than with one, although litter size is larger. Three breedings during the fertile period do not increase whelping rates above two breedings, but there may be a slight increase in litter size. Daily cjaculation diminishes sperm numbers dramatically by the second day, whereas semen collection every other day does not have such a profound effect on sperm numbers. On average 4 to 10 days of ejaculation deplete the extragonadal sperm reserves in the epididymis and ductus deferens. Thereafter the number of sperm per ejaculate is substantially less than half the number collected on the first day. This could be an important consideration for a very popular stud and when semen is being collected for freezing. Results from breeding during the fertile period with semen of good quality are optimized when bitches are 6 years of age or younger and dogs are 8 years of age or younger.

#### **Artificial Insemination**

Artificial insemination (AI) is used in dogs primarily when natural breeding cannot be accomplished. Transporting semen, rather than live animals, to distant geographic locations is a great advantage of AI over natural service. AI is also used when behavioral problems, such as partner preference, or physical problems, such as vaginal prolapse, prevent copulation of the desired pair. Some dog breeders prefer AI because they believe that the risk of breeding trauma is minimized and that the stud is less likely to be exposed to infectious diseases carried by the bitch. In addition, a single ejaculate with sufficient numbers of spermatozoa can be divided and used to inseminate several bitches. The success of AI is determined by several factors, including the reproductive health of the animals, the quality of the semen, the timing and the number of inseminations, intravaginal versus intrauterine insemination, and the technical skills of the person performing the insemination.

It is important to document semen quality before insemination because the success of the insemination will be no better than the quality of the semen. Knowing that semen quality is poor, the owner may wish to use a different stud. Although pregnancies are occasionally achieved using fresh semen of inferior quality, the litter size is usually smaller. Usually, no litters result if frozen-thawed semen of poor quality is used. In addition, once inseminated, the bitch should not be bred to a different male during that cycle because paternity is uncertain unless DNA testing is done. Two inseminations should be performed at the optimal time during the fertile period, as discussed in Chapter 56. It has been shown that pregnancy rates from AI are improved when the semen is deposited directly into the uterus rather than into the cranial vagina. This is especially important when frozen-thawed semen is used because, relative to fresh or chilled semen, the frozen-thawed spermatozoa have a very short life span and poor ability to transverse the cervix. It has been estimated that to achieve similar pregnancy rates with frozen-thawed semen, at least 10 times the number of viable sperm are needed for vaginal AI than for intrauterine AI. Intrauterine insemination can be accomplished transcervically using specially developed catheters (Norwegian catheter; Norske Pelsdyrforlag A/L) or endoscopically. These transcervical insemination techniques are commonly referred to as TCI. Intrauterine insemination can also be accomplished via laparoscopy or through a mini laparotomy.

While the semen is being handled, it must be protected from sudden changes in temperature. Freshly ejaculated canine semen is most effectively protected against temperature shock by working at room temperature and inseminating promptly after collection. Pregnancy rates of 84% have been achieved with vaginal AI of fresh semen. Chilled and frozen semen are protected against damage during processing by the addition of a protective "semen extender" to the sample and by careful attention to the cooling, freezing, and thawing rates. Semen extenders have been formulated to provide nutritional support for the sperm cells, buffer pH changes that occur because of continued metabolic activity, maintain physiologic osmotic pressure, prevent bacterial growth, protect cells from cold shock during chilling, and limit cell damage during freezing and thawing.

The advantage of chilled extended semen over natural breeding or AI with fresh semen is that the semen, rather

than the animals, can be transported. The advantage of chilled semen over frozen semen is that the pregnancy rates are better. Pregnancy rates and the longevity of chilled semen vary tremendously according to the type of extender and processing methods used. Properly extended and cooled semen of good quality can be stored at 5°C for 12 to 24 hours and usually longer. Recently, new extenders have been developed that maintain sperm viability for 1 to 2 weeks at 5°C (www.canirep.com). It is important to follow the instructions for warming chilled semen before insemination because the methods will vary according to the extender used. Pregnancy rates of 50% to 70% are reported for the use of various extenders with chilled semen and vaginal insemination. Whelping rates can be improved from about 45% with vaginal AI to about 65% with intrauterine AI using chilled semen. Extender, equipment, and instructions for their use and for collecting, chilling, and inseminating semen are available from several commercial sources (Fresh Express ICG, Synbiotics; Cryogenetics Laboratory of New England; International Canine Semen Bank; Canine Cryobank; www. canirep.com).

The greatest advantage of frozen semen is that cryopreservation is the only way in which the genetic potential of valuable male animals can be saved indefinitely. Using frozen semen, litters can be sired by a dog long after his death. Another advantage is that semen can be collected and stored whenever it is convenient to do so, in contrast to fresh or chilled semen, in which the timing is determined by the availability of cycling females. Conception rates achieved using frozen semen vary according to the extender and the sperm-processing techniques used (pellets versus straws, freezing rates, thawing rates). Pregnancy rates achieved with vaginal insemination using frozen-thawed semen of good quality have been about 30%, whereas pregnancy rates of 50% to 80% have been achieved when intrauterine insemination has been performed. The frozen semen should be accompanied by information from the collection and storage facility regarding the number of sperm in each straw or vial and the recommendations for thawing the semen. The latter is important because the ingredients in the extender influence the ideal thawing rates and temperatures, which have a significant effect on the postthaw motility. For additional information on AI and regulations for international shipment of chilled and frozen canine semen, the reader should consult the International Veterinary Information Service (www.IVIS.org).

# DIAGNOSTIC TECHNIQUES TO ASSESS REPRODUCTIVE FUNCTION

# **SEMEN COLLECTION AND EVALUATION** Indications

Semen is collected and evaluated as a routine part of a breeding soundness examination, for evaluation of male infertility, when artificial insemination is to be performed, and when semen is to be preserved by chilling or freezing. Cytologic

evaluation of the ejaculate is also used to evaluate diseases of the prostate, testes, and epididymides.

#### **Technique**

Many factors affect semen quality, including the animal's age, testicular size, frequency of ejaculation, degree of sexual arousal, collection technique, and the amount of seminal fluid collected. Semen is easily collected from dogs, especially those with previous breeding experience. The collection area should be quiet and free from distractions, with secure footing for the animals. The dog is encouraged to ejaculate by rapid massage of the bulbus glandis through the prepuce. The presence of an estrous bitch will improve the quality of the ejaculate and the ease with which semen is collected (libido). It has been shown that prostaglandin  $F_{2\alpha}$  (Lutalyse<sup>®</sup>, Pfizer) 0.1 mg/kg, administered subcutaneously 15 minutes before collection, increases the number of sperm ejaculated, similar to the presence of an estrous bitch. It may also have a positive effect on libido. When prostaglandin F<sub>2n</sub> and an estrous teaser bitch are both used, the effects are additive and the number of sperm ejaculated may be increased by nearly 300% (Root Kustritz et al., 2007). Side effects of prostaglandin  $F_{2\alpha}$  are transient and mild but also common. They include salivation, defecation, and vomiting. Semen can also be collected by electroejaculation, but this is rarely necessary in domestic dogs. Semen is usually collected from cats by electroejaculation under general anesthesia, although some cats can be trained to accept an artificial vagina. Feline semen collection and evaluation are not usually performed in clinical practice, but assisted reproduction techniques are used extensively in the study of endangered feline species.

Canine semen is ejaculated in three fractions. The first fraction, or presperm fraction, is composed of a few drops of clear fluid that originates from the prostate. Although this is uncommon, certain dogs may ejaculate several ml of the presperm fraction. The second fraction is the sperm-rich fraction. The volume of the sperm-rich fraction varies from 0.5 to 5 ml, depending on testicular size and individual variation. The sperm-rich fraction appears cloudy and opalescent. Usually, no attempt is made to separate the first two fractions. The third and largest fraction is prostatic fluid, of which there may be as much as 30 ml. Normal prostatic fluid is clear and easily distinguished from the milky, sperm-rich fraction. For routine semen evaluation and artificial insemination, it is sufficient to collect only enough prostatic fluid to ensure that the entire sperm-rich fraction has been obtained.

There are a variety of sophisticated methods that can be used to assess the structure and function of spermatozoa. These include various staining techniques to evaluate viability, the integrity of the plasma membrane, the capacitation status, and the acrosome reaction. There are in vitro assays to assess sperm functions, such as the ability to stimulate the acrosome reaction, measuring the ability of sperm to bind to the zona pellucida, or determining the ability to penetrate the oocyte. Computer-assisted sperm analysis programs have

been adapted for use with canine semen. These programs can assess sperm motility and morphology. At this time uniform laboratory standards for adapting these procedures to canine semen have not been established, and the correlation of specific findings with in vivo fertility has not been determined. Nevertheless, these methods have important potential application, especially for semen freezing centers. Scanning and transmission electronmicroscopy continue to be useful for evaluation of sperm morphology.

In clinical practice semen evaluation focuses primarily on sperm numbers, morphology, and motility. These parameters are often referred to as the spermiogram. A complete cytologic evaluation of other cells (e.g., white blood cells, red blood cells, epithelial cells) in the seminal fluid is also important. In cases of azoospermia determination of seminal fluid alkaline phosphatase is indicated. Because feline semen is rarely evaluated in clinical practice, the interested reader is referred to Zambelli (2006b) and Johnston (2001) for additional information (see Suggested Readings). Semen must be handled carefully. All equipment should be clean and free of contaminants, including water and excessive lubricant. The sample must be protected against sudden changes in temperature. Normal dog semen can usually be handled at room temperature for 10 to 15 minutes without adverse effects. Nevertheless, the sample should be processed promptly. Slides and coverslips should be maintained at 37°C.

# Motility

Assessment of motility is usually the first step in semen evaluation because it must be assessed promptly after collection so that changing temperature does not slow motility. Although not a precise measure, assessment of motility is considered a critical part of semen evaluation because it gauges spermatozoal function and viability. Very poor samples can be distinguished from very good ones. A decrease in the percentage of motile sperm is one of the first detectable changes after testicular injury. Asthenozoospermia is the term used to denote low motility. The percentage of motile sperm and the vigor of the movement can be spuriously diminished if the sample is exposed to excessive heat or cold, contaminated equipment, inflammatory cells, or bacteria. Poor motility may also be found in the setting of incomplete ejaculation. The motility of sperm ejaculated after a long sexual rest may also be poor because of aging of the cells. In addition, sperm in semen that has been chilled or frozen usually does not regain its original motility when warmed. In the case of chilled semen, the percentage of motile sperm may be similar to that seen in the fresh semen, but the individual sperm usually move with less vigor. Both the percentage and the speed of motility are usually diminished in frozen-thawed semen. Side-to-side oscillation may be a reflection of cooling, or it may be an artifact, representing the jostling of nonmotile sperm by motile ones.

To assess spermatozoal motility, a drop of undiluted semen is placed on a warm slide, covered with a warm coverslip, and examined by phase-contrast or light microscopy using the 40× and 100× objectives. Very concentrated samples should be diluted with warm 2.9% sodium citrate or phosphate-buffered saline solution to permit careful evaluation of individual spermatozoa. The percentage of motile sperm and the vigor of their movement are then estimated. In the normal dog more than 70% of the sperm should show rapid, steady, progressively forward motility. Although normal parameters for the feline spermiogram have not yet been adopted, reports of semen collected by electroejaculation and artificial vagina describe 60% to 85% progressively motile sperm. Spermatozoa that move in circles or in another nonlinear manner usually do so because of morphologic defects in the tail or midpiece.

#### Morphology

The sperm head is composed of the nucleus, which is covered proximally by the acrosome. The equatorial segment of the head represents thinning of the acrosome. The postacrosomal sheath and cell membrane cover the sperm head distally. The sperm tail is composed of the neck, midpiece, principal piece, and end piece. Often, the principal piece and end piece are collectively referred to as the tail. The neck is composed of laminated fibers and implantation plates that connect the midpiece to the head at the implantation fossa. A mitochondrial helix surrounds the axoneme of the midpiece. The axoneme is composed of nine microtubule doublets surrounding a central pair of singlet microtubules. A fibrous sheath of nine outer dense fibers surrounds the axoneme of the principal piece. The outer dense fibers gradually dissipate, and the end piece begins where the fibrous sheath ends. During spermatogenesis residual cytoplasm is extruded at the level of the midpiece.

Teratozoospermia refers to abnormal spermatozoal morphology. Morphologic abnormalities are sometimes classified as being primary or secondary or as being major or minor. Primary abnormalities are usually attributed to abnormal spermatogenesis in the testicle, whereas secondary abnormalities are attributed to errors in epididymal maturation or improper sample handling. Because the morphologic abnormality does not always reflect the site of the lesion, the abnormality should be described specifically (e.g., bent tail). Abnormalities are also classified according to their likely effect on fertility as being of either major or minor importance (Table 60-1). Abnormalities in the size and shape of the head, acrosome, midpiece, or proximal tail, and proximal droplets are usually considered the most severe (Fig. 60-2). Loose or detached heads, or acrosomes that are otherwise normal, distal droplets, and bent tails are considered less severe, although they may be the first abnormalities noted after a testicular insult. These classifications were developed for evaluation of fresh semen. The relative significance of some abnormalities, such as the acrosomal reaction, may differ in frozen-thawed semen because they may then reflect irreparable damage during processing.

Morphology can be assessed in unstained samples using phase-contrast microscopy. Many abnormalities can also be seen in unstained samples using routine light microscopy with properly adjusted light intensity and low condenser



**TABLE 60-1** 

### Classification of Morphologic Defects in Canine Spermatozoa

CLASSIFICATION	LOCATION			
	HEAD	MIDPIECE	TAIL	
Major	Macrocephalic; microcephalic Pyriform (pear shape) Nuclear vacuoles (diadem or crater defect) Binucleate (ridged sperm) Double head Acrosomal condensation (knobbed, nipple)	Proximal cytoplasmic droplet Kinked Bent (reflex) Ruptured All abnormalities except distal droplet	"Dag" defect Double tails	
Minor	Detached, otherwise normal, heads Nuclear condensation Swollen or detaching acrosome	Distal cytoplasmic droplet	Bent Simple coiling	

From Oettle EE, 1995.

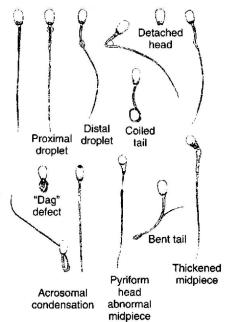


FIG 60-2
Morphologic appearance of canine spermatozoa.

position, but more information can be gained when the samples are stained. Although many stains can be used to evaluate sperm morphology, in veterinary medicine the most common are eosin-nigrosin stains (e.g., Society for Theriogenology morphology stain). In dogs and cats modified Wright's stain (Diff-Quik®, VWR Scientific Products) is a better choice because there is less chance of stain-induced artifact in canine semen, and the staining characteristics using Diff-Quik correlate well with biomarkers of feline spermatozoal health (Mota et al., 2006). Another advantage over eosin-nigrosin stains is that other cells, such as red blood cells and white blood cells, are also stained and easily recognized. Stained slides are examined microscopically under oil immersion. A minimum of 100, but preferably 200,

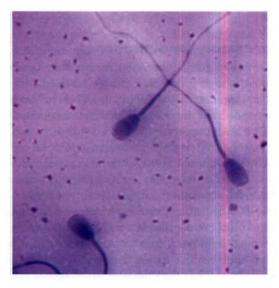


FIG 60-3 Canine sperm stained with Diff-Quik.

spermatozoa is classified as being normal or abnormal (Figs. 60-2 to 60-4). Fewer than 20% of the spermatozoa in semen samples from normal dogs have morphologic abnormalities. Electron microscopy may provide additional useful information in selected cases.

Bent tails deserve special mention because they may be artifactually induced by cold shock and by stain or diluent of improper pH or osmolality. Finding excessive numbers of bent tails in a sample previously assessed as having had normal motility strongly suggests the possibility that the bent tails were caused by the stain because sperm with bent tails usually cannot move with a straight, forward progression. Stain-induced abnormalities and those resulting from improper sample handling should not be found in subsequent, properly handled aliquots of the sample. Persistence of morphologic abnormalities is an indication for further diagnostic evaluation, including semen culture.

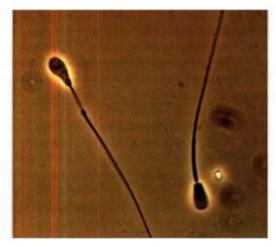


FIG 60-4
Canine spermatozoa with pyriform head and abnormal midpiece; phase-contrast microscopy. (Courtesy Dr. Patricia Olson, Morris Animal Foundation, Englewood, Colo.)

# **Spermatozoa Concentration**

The number of normal motile sperm has a direct effect on fertility. Although pregnancies can be achieved with fewer sperm, a minimum of 200 million motile sperm are usually recommended for intravaginal artificial insemination in dogs. Doing so is expected to yield normal pregnancy rates and litter size. Fewer numbers of sperm or samples with high numbers of abnormal sperm yield lower pregnancy rates and/or smaller litter size. The negative effects of some sperm defects can be overcome (compensated for) by increasing the number of sperm inseminated, whereas others cannot. In dogs the volume of the ejaculate and thus the concentration of sperm are influenced most by the volume of sperm-free prostatic fluid. For this reason the number of sperm in the total ejaculate, rather than the number of sperm per ml of semen, is assessed. The number of sperm is determined using a hemocytometer. The sample to be counted is usually diluted 1:100 using white blood cell/platelet dilution pipettes (Unopette; Becton-Dickinson and Co.). It may be unnecessary to dilute oligozoospermic samples before counting. To calculate the number of sperm per ejaculate, the number of sperm per ml as determined by the hemocytometer is multiplied by the total volume (ml) of the sample collected. Spectrophotometric methods may also be used to determine the sperm count. The number of sperm per ejaculate in normal dogs is  $300 \times 10^6$  to  $2000 \times 10^6$ . Average counts of 30  $\times$  10<sup>6</sup> to 300  $\times$  10<sup>6</sup> sperm per ejaculate are reported for cats.

There is great interdog and intradog variation in the number of sperm in any given ejaculate from normal fertile dogs. The breed of dog, size of the testes, degree of arousal, and frequency of ejaculation affect the number of sperm ejaculated. Because the spermatogenic potential is directly related to testicular size, smaller breeds of dogs are expected to have fewer sperm per ejaculate than large breeds of dogs. Although it has been stated that sperm production is also directly related to body weight, this holds only for animals

in normal body condition. The relationship between sperm production and body weight is lost in obese dogs. Daily ejaculation depletes extragonadal reserves from the epididymis and ductus deferens, causing an immediate and dramatic reduction in the number of sperm ejaculated, but in normal males the numbers are often still within the normal range. To minimize this effect, at least 1 day, and preferably 3 to 4 days, should elapse between collections. This is especially important for semen being collected for freezing and for subfertile males in any setting. As a general rule, a total number of less than  $200 \times 10^6$  sperm in any sample from a mature dog should be considered abnormally low (oligozoospermic), regardless of the breed of dog.

## **Volume**

The volume of seminal fluid, and therefore the concentration of the sperm, varies according to collection technique. Typically, electroejaculation yields higher volume and lower concentration than does the use of an artificial vagina. The seminal volume is determined directly from the calibrated tube into which the sample is collected. Volumes tend to be smaller in young dogs than in mature dogs. Volume does not usually correlate with fertility unless the animal fails to ejaculate an adequate amount of the sperm-rich fraction. For intrauterine AI in bitches, a volume of 4 ml or less is used. This is accomplished by centrifugation of the sample to concentrate the number of sperm/unit volume.

#### Color

The color is assessed by direct visualization. Dog semen is normally white to opalescent and opaque. Inflammatory cells and squamous epithelial cells may also cause the seminal fluid to be opalescent. Inflammatory cells can originate from anywhere in the urinary or genital tracts, including smegma from the preputial cavity. Yellow seminal fluid usually indicates the presence of urine. To avoid urine contamination, dogs should not be allowed to micturate immediately before semen collection. Some males urinate during ejaculation, which is not normal. They are usually subfertile. Red or redbrown semen usually contains blood. Blood in a canine ejaculate usually originates from the prostate, or it results from damage to the surface of the penis during collection. The latter source of hemorrhage can easily be excluded by prompt inspection of the penile surface. Complete cytologic evaluation of the semen is important, especially in cases of infertility and when the sample has an abnormal color.

#### Cytology

In addition to the spermatozoa, all cells in the semen sample should be evaluated. Cytologic examination of the third fraction of the ejaculate is very helpful in the evaluation of canine prostatic disorders. A finding of red blood cells indicates hemorrhage, whereas a finding of white blood cells and macrophages indicates inflammation somewhere in the urogenital tract. Fewer than 2000 white blood cells per ml, or up to 7 white blood cells per high power field, is considered normal in canine semen. Dogs with leukospermia should be

tested for *Brucella canis* (see Chapter 58), and the semen should be cultured for aerobes, anaerobes, and *Mycoplasma*. Some epithelial cells are normally present in dog semen, and their numbers increase with sexual rest. They are also present in the prepuce and on skin. Crystals may be found in samples contaminated with urine or with talc from the collection equipment. When excessive numbers of cells other than spermatozoa are found, further diagnostic assessment of the urogenital tract may be warranted.

# Seminal Alkaline Phosphatase

Alkaline phosphatase is produced in the canine epididymis and the feline testis and/or epididymis. Therefore the enzyme can be used as an indicator that epididymal fluid, which should contain high numbers of motile sperm, is present in the sample. The seminal alkaline phosphatase activity in whole semen from normal dogs may be as high as 4000 to 5000 IU/L or greater and greater than 100,000 IU/L in cat seminal plasma. Azoospermia with low seminal alkaline phosphatase activity may indicate bilateral obstruction distal to the epididymes, or ejaculation may have been incomplete. Azoospermia with high alkaline phosphatase indicates failure of sperm production or bilateral obstruction at the rete testis. Alkaline phosphatase activity in seminal fluid is determined by the same methods used to determine alkaline phosphatase activity in serum.

# Seminal pH

In some species changes in the seminal pH have diagnostic significance. The pH of canine seminal fluid and of prostatic fluid normally ranges from 6.3 to 7.0 and from 6.0 to 7.4, respectively, even in the presence of genital tract disease. Therefore determination of the seminal or prostatic fluid pH is rarely of diagnostic importance in dogs. Feline seminal fluid has a pH of about 6.6.

#### Interpretation of Semen Evaluation

The seminal characteristics thought to correlate best with fertility are the total number of sperm per ejaculate and the motility and morphology of spermatozoa. The quality of a canine semen sample is a reflection of (1) spermatozoal production during the past 62 days; (2) epididymal maturation during the past 14 days; (3) the extragonadal sperm reserves, which may take up to 7 days to be replenished in normal dogs; and (4) the spermatozoal output of that particular ejaculation. The finding of normal semen is not proof of normal fertility, however, because the male must also have normal libido and normal mating ability. Nevertheless, a dog with normal semen is expected to successfully impregnate a bitch if other factors are favorable. Likewise, the finding of abnormal semen does not necessarily indicate sterility unless there is persistent azoospermia or complete, true necrozoospermia. Even males with normal fertility, as demonstrated by breeding trials, may on occasion have a sample that is not within the expected normal ranges, particularly with regard to total sperm count. However, evidence shows that when fewer than 60% to 80% of the sperm are morphologically normal or when progressive motility is less than 50%, canine pregnancy rates are poor. Although it has been stated that prolonged abstinence contributes to poor semen quality because of spermatozoa senescence, it is unlikely that abstinence alone causes the quality of previously normal semen to diminish to the point of oligozoospermia and less than 60% normal morphology and motility. To help establish a prognosis or to resolve doubt about the cause of an unsatisfactory sample, the dog should be reevaluated several times over a period of at least 2 months. Recovery from a testicular insult may not be reflected by improved seminal quality for more than 3 to 5 months.

#### **BACTERIAL CULTURE OF SEMEN**

Quantitative and qualitative culture of the semen is indicated (1) as a routine part of the diagnostic evaluation of infertility in the male; (2) when excessive numbers of inflammatory cells are identified in the semen; and (3) in dogs with suspected bacterial prostatitis, epididymitis, or orchitis. Clinically significant growth of >10<sup>5</sup> colony-forming units (CFUs) of aerobic and anaerobic bacteria and Mycoplasma are recovered from more than half of normal fertile dogs that have no cytologic evidence of inflammation in the seminal fluid. Conversely, 30% of aerobic cultures from dogs with large numbers of white blood cells in the seminal fluid yielded no growth. For these reasons it has been recommended that semen culture be included as a routine part of the evaluation of canine infertility, irrespective of cytologic findings suggestive of infection. For culture results to be meaningful, an aseptic technique and sterile collection devices should be used. To limit contamination from the preputial cavity, the preputial orifice should be cleansed and smegma flushed off the surface of the penis before semen is collected. The spermrich fraction and the prostatic fraction of the canine ejaculate should yield fewer than 100 CFUs of bacteria per milliliter, whereas normal feline seminal plasma may contain more than 10,000 CFUs of bacteria. Results of semen cultures must be interpreted in conjunction with the clinical signs, the results of the cytologic evaluation of the ejaculate, and the variety of species of bacteria grown.

The normal bacterial florae of the prepuce and distal urethra are the same organisms most frequently isolated from normal canine and feline semen and from dogs with bacterial prostatitis, orchitis, or epididymitis. The normal florae of the distal urethra and prepuce consist predominantly of aerobic organisms, but anaerobic organisms are also found. Pasteurella multocida, β-hemolytic Streptococci, and Escherichia coli are the organisms most commonly isolated from dogs, whereas β-hemolytic E. coli, Pseudomonas aeruginosa, and Proteus mirabilis are the most common in cats (Boxes 60-1 and 60-2). The number of CFUs per milliliter of semen attributable to urethral contamination reportedly varies from 100 to 10,000. A separate culture of the material from a urethral swab, obtained before ejaculation, can be used to identify urethral organisms. Alternatively, the first fraction and the initial portion of the second fraction of the canine ejaculate can be discarded (i.e., not



BOX 60-1

#### Bacterial Isolates from the Prepuce and Semen of Stud Dogs

Prepuce	Semen	Semen
(n = 232 samples from 15 dogs; Bjurström et al)	(n = 232 samples from 15 dogs; Bjurström et al)	(n = 95 dogs; Root Kustritz et al., 2005)
Pasturella multocida	Pasteurella multocida	Aerobic Organisms in 28% of Samples
β-hemolytic Streptococci	β-hemolytic <i>Streptococci</i>	β-hemolytic <i>Streptococci</i>
E. coli	E. coli	Pasteurella multocida
Coagulase neg Staphylococci	Pasteurella spp.	β-hemolytic <i>E. coli</i>
Staphylococcus intermedius	Streptococcus spp.	nonhemolytic E. coli
Streptococcus spp.	Staphylococcus intermedius	Achromobacter
Pasteurella spp		Actinomyces pyogenes
Coryneforms		Bacillus spp.
Enterococci		Coagulase pos Staphylococcus
Pseudomonas spp.		Hemophilus
Proteus		Klebsiella
		Proteus
		Pseudomonas
		Staphylococcus intermedius
		Anaerobic Organisms in 14% of Samples
		Bacteroides spp.
		Peptostreptococcus
		Propionibacterium
		Clostridium
		Fusobacterium
		Streptococcus morbillorum
Mycoplasma present in 11% of samples and 80% of dogs	Mycoplasma present in 3% of samples and 27% of dogs	Mycoplasma present in 58% of samples
No bacterial growth in 14% of samples	No bacterial growth in 70% of samples	No bacterial growth in 18% of samples

submitted for culture). The number of urethral organisms contained in the later seminal fractions then tends to be reduced. Separately culturing each fraction of the canine ejaculate may help show whether the infection is in the testes and epididymis (second fraction) or in the prostate gland (third fraction). In most dogs the first fraction consists of only a few drops of fluid and is difficult to separate from the second fraction.

In dogs with epididymitis or orchitis, a culture specifically for *Brucella canis* should be requested (see Chapter 58). Specimens for anaerobic, *Mycoplasma*, and *B. canis* culture must be handled promptly and carefully because these organisms are sometimes more difficult to isolate than aerobes. The veterinarian should contact the microbiology laboratory to obtain specific recommendations concerning the submission of these samples. Special media, such as Anaerobic Culturette (Becton-Dickinson), is often recommended. Despite widespread concern among dog breeders, the role of *Mycoplasma* as a spontaneous cause of canine infertility remains to be fully clarified (see Chapter 58).

#### DIAGNOSTIC IMAGING

In the evaluation of male reproductive disorders, radiography is used primarily to assess the size of the prostate gland

and identify metastatic lesions in dogs with suspected prostatic adenocarcinoma. Ultrasonography is very useful to identify and characterize lesions within the prostate, testis, and epididymis; to help determine the cause of testicular or scrotal swelling; to assess the character of the spermatic cord in suspected cases of torsion; and to help establish the location of undescended testes. Ultrasonography is routinely used to guide biopsy needles for obtaining specimens from the prostate gland and focal lesions within the testis or epididymis.

# **HORMONAL EVALUATION**Testosterone

Testosterone is produced by the interstitial (Leydig) cells of the testes, under the control of LH and GnRH. It is secreted in a pulsatile manner that occurs about every 80 minutes in male dogs. In normal male cats the nadir concentrations may be below the levels of detection of some assay systems. There is also a diurnal rhythm, with the lowest serum concentrations in the morning and the highest at night. The serum testosterone concentration is most frequently measured to determine the presence and functional status of the testes. It is useful to differentiate previously castrated males from those with bilateral cryptorchidism or those in which an



BOX 60-2

Bacterial Isolates from the Prepuce and Semen of Tomcats with Normal Semen

#### Prepuce

n = 29 samples β-hemolytic E. coli Pseudomonas aeruginosa Proteus mirabilis Klebsiella oxytoca Streptococcus spp. Nonhemolytic E. coli Enterococcus Bacillus spp. Serratia odorifera Streptococcus enterococcus Staphylococcus spp. Yersinia intermedia

Acinetobacter spp.

samples

No aerobic bacterial

growth in 10% of

#### Semen

n = 29 samples β-hemolytic E. coli Pseudomonas aeruginosa Proteus mirabilis Klebsiella oxytoca Streptococcus spp. Streptococcus enterococcus Nonhemolytic E. coli Staphylococcus spp.

No aerobic bacterial growth in 3% of samples

From Johnston SD et al: Ovarian and testicular function in the domestic cat: clinical management of spontaneous reproductive disease, *Anim Reprod Sci* 42:261, 1996.

intraabdominal testis was left after castration of a scrotal testis. It may also be of interest in evaluation of intersex animals. A single random determination is often not helpful because the nadir concentrations can be very low and values from intact animals may overlap with those for castrated males. Provocative testing is necessary to adequately assess testosterone production. This is done by measuring the serum testosterone concentration before and after the administration of human chorionic gonadotropin (hCG) or gonadotropin releasing hormone (GnRH).

Because the preferred protocols and the reference ranges vary greatly among laboratories, consultation with the laboratory is important. For example, in hCG stimulation protocols the serum testosterone concentration is typically measured before and 2 to 4 hours after the administration of hCG (40 to 50 IU/kg, administered intramuscularly in dogs and cats; or 250 IU per cat, administered intramuscularly). In GnRH stimulation protocols samples are typically obtained before and I hour after administration of GnRH (0.22 µg/kg, administered intravenously in dogs; 1.0 to 2.2 µg/kg, administered intramuscularly in dogs; 25 µg/cat, administered intramuscularly). Reference ranges for intact male dogs from a large veterinary diagnostic laboratory are 2.6 to 13.9 nmol/L and 13 to 17.3 nmol/L, before and after GnRH, respectively. Castrated male dogs and cats have serum testosterone concentrations of <0.5 nmol/L. In contrast, another veterinary diagnostic laboratory's ranges for intact male dogs are 0.19 to 26.3 ng/ml and 0.46 to 22.1 ng/ml and for castrated dogs 0.01 to 0.24 ng/ml and 0.02 to 0.42 ng/ml, before and after hCG, respectively; and the reference range for serum testosterone concentrations in castrated cats overlaps that of intact male cats (0.10 to 2.3 ng/ml versus <0.5 ng/ml, respectively).

Finding high serum concentrations of testosterone, with or without the administration of hCG or GnRH, indicates the presence of at least one testicle. Animals with only one testis and intersex animals may have testosterone values between those typically found in castrated and intact males after hCG or GnRH administration. Testosterone is sometimes measured in the evaluation of infertile males, but testosterone deficiency is rarely documented as a cause, or effect, of acquired infertility in dogs or cats. Congenital hypogonadism is characterized by abnormally small testes, which lack normal spermatogenesis and testosterone production.

Finding low serum concentrations of testosterone after hCG or GnRH administration in an otherwise healthy male almost always indicates previous castration because Leydig cells are quite resistant to thermal injury, toxic injury such as that caused by chemotherapeutic agents, and infectious agents, unless the entire testicle is destroyed by the process. Low testosterone concentrations could also indicate exposure to drugs such as ketoconazole that interfere with steroid hormone production or drugs that suppress GnRH or LH, such as gonadal steroids or GnRH antagonists (See the section on contraception in Chapter 56). Severe malnutrition can damage Leydig cells.

Because the development and maturation of the penile spines in cats and the prostate gland in dogs are androgen dependent, they serve as bioassays for the presence of DHT. Penile spines begin to appear in intact male cats at about 12 weeks of age; they regress by 6 weeks after castration. The finding of penile spines indicates the presence of testicular tissue and justifies a presumptive diagnosis of cryptorchidism in tomcats that do not have palpable testes in the scrotum. Finding a prostate gland in a supposedly castrated dog that is of normal size for a sexually intact dog indicates either prostatic neoplasia or the presence of a retained testicle. Administration of exogenous androgens would be another possible explanation in both species.

# Gonadotropins: Follicle-Stimulating Hormone and Luteinizing Hormone

The gonadotropins FSH and LH are produced by the pituitary under the control of hypothalamic GnRH (see Chapter 56; Fig. 56-4). They are secreted in a pulsatile manner. LH pulses occur about every 100 minutes during daylight hours and approximately every 80 minutes during darkness. FSH supports Sertoli cell function and spermatogenesis. LH stimulates testosterone secretion by the Leydig cells of the testis. The gonadal hormones, in turn, feed back to the hypothalamus and pituitary. After gonadectomy this negative feedback control of the gonadotropins is lost, and serum concentrations of LH and FSH are persistently elevated. This could also occur with the rare condition of gonadal dysgenesis. Serum LH concentration in normal male dogs reportedly

ranges from 0.2 ng/ml to less than 20 ng/ml. Normal FSH concentrations in healthy dogs reportedly range from 20 to 293 ng/ml.

To avoid unnecessary laparotomy, serum concentrations of LH can be measured to determine the presence or absence of gonads in animals with unknown reproductive status, such as those newly acquired by shelters or private owners. Males with very high LH have been castrated. Males with low LH have one or both testicles. If the testes are not in the scrotum, the male is cryptorchid. Much less likely causes of low LH would be exposure to exogenous sex hormones or a hypothalamic-pituitary lesion causing hypogonadotropic hypogonadism. Males with hypogonadism have abnormally small testes with diminished (or absent) spermatogenesis and testosterone production. The secretory capacity of the pituitary gonadotropins can be assessed by determining LH and/or FSH before and after administration of GnRH. A point-of-care, semiquantitative immunochromogenic assay for LH (ICG Status-LH®, Synbiotics) has been intermittently available. Few commercial laboratories offer validated quantitative assays for LH or FSH for veterinary species at this

#### **TESTICULAR ASPIRATION AND BIOPSY**

Testicular biopsy or aspiration and epididymal aspiration are usually reserved for animals that have been thoroughly investigated by other noninvasive means but in which no cause of infertility has been identified. Aspiration, biopsy, or both are indicated early in the evaluation of animals with discrete, focal lesions or in those with marked changes in the consistency of the testis or epididymis. The cytologic evaluation of testicular aspirates can identify inflammatory cells, sperm, neoplastic cells, and infectious agents. Testicular aspiration is usually reserved for the evaluation of discrete lesions rather than the assessment of spermatogenesis because tissue architecture is not preserved and the progression of spermatogenesis cannot be assessed. Fine-needle (i.e., 25 gauge) aspiration of the testes is performed in a manner similar to the aspiration of other masses. Sedation may be required in some dogs and is usually recommended for animals undergoing epididymal aspiration. In the absence of equipment to collect semen from cats, cytologic evaluation of a testicular aspirate could be used to confirm the presence of sperm.

Seminiferous tubule architecture, the progression of spermatogenesis, and interstitial and Sertoli cell numbers can be evaluated in specimens obtained by biopsy. Histopathology can also be used to determine whether there is inflammation or neoplasia within the testicular parenchyma. It has been shown that biopsy of a normal testis has no deleterious effect on semen quality in normal dogs. General anesthesia is required for animals undergoing testicular biopsy. The initial surgical approach is similar to that used for open castration except that the testis is not lifted out through the skin incision. When the proper vaginal tunic and the adherent tunica albuginea are incised, normal testicular tissue promptly bulges through the incision site. This bulging testicular tissue is excised for histopathologic and microbiologic evaluation.

The proper vaginal tunic/tunica albuginea is closed. Then the common vaginal tunic is closed, the testis is replaced in the scrotum, and the closure is as in a routine castration. Alternatively, the skin is incised with a scalpel, the testis is immobilized, and a biopsy needle is pushed through the tunic into testicular tissue. Incisional biopsy provides larger tissue specimens than does needle biopsy, but this method also causes greater damage to testicular parenchyma. Testicular tissue for histopathologic evaluation must not be fixed in formalin because artifacts are produced. Zenker's, Bouin's, glutaraldehyde, and Karnovsky's fixative are recommended, depending on whether tissues are to be embedded in paraffin or plastic. Some clinicians prefer glutaraldehyde over Bouin's for the epididymis. It is recommended that the pathologist be consulted regarding the preferred fixative before obtaining the specimen.

Complications from testicular aspiration or biopsy are not common if a careful, gentle, and aseptic technique is used. However, some of the potential complications could adversely affect the future fertility of the dog. These include swelling, local hyperthermia, infection, hemorrhage, and the formation of sperm granulomas. We routinely rinse away residual scrub solutions and apply an ice pack to the biopsy site while the dog is recovering from anesthesia to minimize swelling and local skin irritation. All pertinent noninvasive tests should be performed before biopsy is considered.

Noninflammatory, degenerative conditions of the testes vary in severity from diminished spermatogenesis to a complete absence of germ cells and collapse of the seminiferous tubules. Sometimes, only Sertoli cells remain. The less severe lesions are potentially reversible if the underlying cause can be eliminated. Unfortunately, the histologic appearance of testicular specimens obtained from animals with degenerative conditions of the testes rarely indicates the initiating cause. Chemical toxins and thermal and radiation injury can all cause testicular degeneration that may progress to testicular atrophy. The Leydig and Sertoli cells may be spared. Libido is maintained if the Leydig cells are not affected. Chronic testicular infection can also result in testicular degeneration. In this event evidence of the etiologic agents and inflammation may no longer be present.

Suppurative inflammation of the testes is characterized by infiltration of neutrophils. Macrophages and giant cells may also be found. Bacterial or mycotic infections are the usual cause. Viral orchitis, which occurs in some species, has not been reported in dogs. Immune-mediated reactions to sperm, mycotic infection, and *Brucella canis* infection are the most common causes of granulomas in the canine testicle.

If lymphocytes and plasma cells are found, the orchitis is usually thought to be immune mediated, but this does not exclude the possibility that infection was the initiating cause. For example, chronic *B. canis* infection is characterized by lympho-plasmacytic inflammation that is thought to be caused by antisperm antibodies produced as a result of the infection. Because the antigens that are unique to spermatozoa are usually not accessible to immune surveillance, any-

thing that disrupts the integrity of the seminiferous tubules or the blood-testis barrier has the potential to expose sperm antigens and incite an immune response. By this mechanism, testicular trauma, infection, or neoplasia may cause lymphocytic orchitis. Often, the cause of canine lymphocytic orchitis is not found, and sterility ultimately occurs. Foci of lymphocytes can be found in testicular biopsy specimens from apparently normal cats of all ages. The significance of these is unknown, but they are most prevalent in cats older than 8 to 9 years of age.

# DIAGNOSTIC APPROACH TO INFERTILITY

Normal seminal quality, normal desire to breed (libido), and normal ability to mate are all necessary for normal fertility in males. Therefore the diagnostic approach to infertility must investigate all three of these factors (see Fig. 60-5). Dogs achieving pregnancy rates of less than 75% when bred to apparently normal females using proper breeding management should probably be evaluated for subfertility because pregnancy rates of 85.4% ± 12.4% have been reported for privately owned, fertile stud dogs in which two matings per estrus were done. Pregnancy rates of greater than 90% are expected in well-managed commercial breeding colonies because individual animals with poor fertility are likely to be promptly culled.

The diagnostic approach begins with a complete history and physical examination. The history should assess the male's past breeding performance, breeding management, fertility of the females to which he has been bred, and current or previous health problems (Box 60-3). Some common drugs and metabolic disorders that are known to affect male fertility are listed in Box 60-4.



BOX 60-3

#### Historical Information for Male Infertility

1. Previous breeding performance

Libido

Mating ability

Dates of breeding, the outcome, and litter size

- 2. Results of previous semen evaluation
- 3. Previous breeding management

Methods of insemination

Date of insemination chosen by

Predetermined day of season?

Behavioral changes?

Vaginal cytology findings?

Ovulation timing?

4. Fertility of the female

Previously produced pups?

Subsequently produced pups?

5. Other health problems, test results, and medications

Assessment of the male's libido and mating ability can help narrow the differential diagnoses. A normal male may appear to lack libido if it is not in its established territory, if it is less dominant than the female or another male in the immediate vicinity, if it is inexperienced or frightened, or if it prefers a different partner. Some normal males show no interest until the female is actually in estrus, as opposed to proestrus. Dogs that are accustomed to semen collection may no longer be interested in natural service despite normal arousal and a willingness to ejaculate. Daily ejaculation, especially over a week or two, and ejaculation more often than once a day are other factors that can diminish the libido of normal male dogs. Frequent ejaculation does not diminish libido in tomcats. Excessive endogenous or exogenous glucocorticoids, stress, and pain also cause decreased libido in dogs. Libido also appears to decrease with advancing age.

Generally, mating ability is determined by physical, mechanical, and neurologic factors governing mounting, erection, intromission, and ejaculation. Orthopedic disorders of the rear legs; spine; and, less commonly, the front legs may prevent mounting or intromission but do not usually affect libido and ejaculatory ability unless they are painful. Semen collection and artificial insemination could be used



BOX 60-4

# Common Drugs and Metabolic Disorders Affecting Male Reproduction

Glucocorticoids

Stress

Exogenous glucocorticoids

Hyperadrenocorticism

Endogenous or exogenous sex steroids

**Progestagens** 

Estrogens

**Androgens** 

Diabetes mellitus

Renal failure

Medications

Anabolic steroids

Cimetidine

Spironolactone

Anticholinergics

Propranolol

Digoxin

Verapamil

Thiazide diuretics

Chlorpromazine

Barbiturates

Diazepam

Phenytoin

Primidone

Ketoconazole

Amphotericin B

Many anticancer drugs

Gonadotropin releasing hormone and gonadotropin antagonists and agonists

in such animals. Some animals may exhibit normal arousal and mount only to dismount before attempting intromission. It is often difficult to determine whether this behavior is caused by inadequate libido or by inadequate mating ability. This behavior is also often exhibited when a vaginal abnormality is encountered and also in some males accustomed to semen collection. Painful conditions often diminish libido as well as interfere with mating ability.

A complete physical examination should be performed to assess the animal's overall health and identify congenital or heritable abnormalities that should be grounds for excluding the male from the breeding program. Many metabolic and physical abnormalities can adversely affect spermatogenesis, libido, and mating ability. The testes and epididymes are palpated to determine their size, shape, consistency, and location. In situations of unilateral disease, there is urgency to establish and correct the cause before the condition affects the contralateral testis. This can occur by direct extension of the disease process itself or as a result of local swelling, pressure, and hyperthermia, all of which are deleterious. Finding abnormally small testes in an infertile male justifies a guarded prognosis for recovery of fertility, irrespective of the underlying cause. Testicular atrophy is common in dogs older than 10 years of age. The American Kennel Club will not register puppies sired by dogs 12 years of age or older without documentation of semen quality. The canine prostate is palpated per rectum and transabdominally. The penis and prepuce are palpated and inspected. Because the penis must be extruded from the prepuce for a thorough examination to be performed, as well as for semen to be collected in dogs, the two are often performed together. This is contraindicated if the history indicates the animal may have a penile lesion that could be aggravated by sexual arousal.

Anatomic abnormalities reported to cause difficulty in mating include phimosis, a persistent penile frenulum, an abnormally short os penis in dogs, and entanglement of the penis in preputial hair in cats. Tomcats that fail to grasp the queen's neck in the proper location may not be in the correct position for intromission. This is seen in some inexperienced males and in mating pairs with disparate body lengths. Male dogs are often reluctant to breed bitches with anatomic abnormalities of the vulva or vagina. Usually, neither shows outward signs of discomfort other than failure to mate; thus it may be difficult to discern whether intromission does not occur because of a female or a male problem.

A thorough neurologic and orthopedic examination should be performed. Neurologic disorders can interfere with mounting, erection, intromission, and ejaculation. For example, motor nerve dysfunction can cause difficulty with mounting and intromission, but semen collection for AI may be possible in such animals. Sensory or autonomic disturbances can cause difficulty with erection (and therefore with intromission in cats) and ejaculation. Semen collection by electroejaculation may or may not be possible in such animals, depending on the location of the lesion.

Semen evaluation is a crucial part of evaluating male infertility (Fig. 60-5). In addition, the semen of infertile

males should be submitted for aerobic, anaerobic, and *Mycoplasma* culture, and *B. canis* testing should be performed in dogs. Males with a history of infertility but that currently have normal semen, normal libido, and normal mating ability are now normal. Such males may have recovered from their previous infertility, the breeding management (e.g., timing of insemination) could have been inappropriate, or the female may have been infertile. Normal males should be bred again to fertile females using optimal breeding management. If the semen is abnormal, further evaluation of the reproductive tract is indicated. Semen is judged to be abnormal if inadequate numbers of sperm are found, if the motility of sperm is inadequate, if sperm morphology is abnormal, or if the semen contains excessive numbers of other cells (white blood cells, macrophages, red blood cells).

Abnormal motility (asthenozoospermia) and morphology (teratozoospermia) are often the first indicators of gonadal damage, irrespective of the cause. Morphologically abnormal sperm often do not have normal motility. Causes include primary testicular disease, metabolic and endocrine disorders, transient insults (e.g., fever), incomplete ejaculation, and iatrogenic causes. Sperm in semen from young dogs and dogs that have not mated for a long time may show poor motility, and the semen may contain more than the usual number of morphologically abnormal sperm. Iatrogenic causes include temperature shock, exposure of the semen sample to a stain of improper pH and osmolality, and exposure of the sample to latex rubber, plastics, and other spermicidal agents.

Infertile animals with abnormal semen should be reevaluated in 4 to 7 days or sooner if an iatrogenic cause is suspected. Care should be taken at that time to ensure that the entire sperm-rich fraction is collected and that improper handling does not damage the sample. If abnormalities persist, semen culture and ultrasound of the reproductive tract are indicated. A metabolic evaluation (e.g., complete blood count, serum biochemistry panel, urinalysis) is also appropriate. If no other abnormalities are identified, semen should be reevaluated in 2 to 3 months before additional testing is done. If the problem persists, additional testing is indicated, as discussed in the section on acquired infertility.

# OLIGOZOOSPERMIA AND AZOOSPERMIA

A decrease in the total number of sperm per ejaculate may occur with or without abnormalities in sperm morphology or motility. Sperm numbers may be less than normal (oligozoospermia), or sperm may be completely absent (azoospermia). The concentration of sperm per ejaculate may decline because of abnormalities in spermatogenesis or ejaculation. The clinician must always exclude the possibility that the entire sperm-rich fraction was not collected before proceeding further. This is ensured by repeat semen collection. In dogs an estrous bitch and the administration of prostaglan-

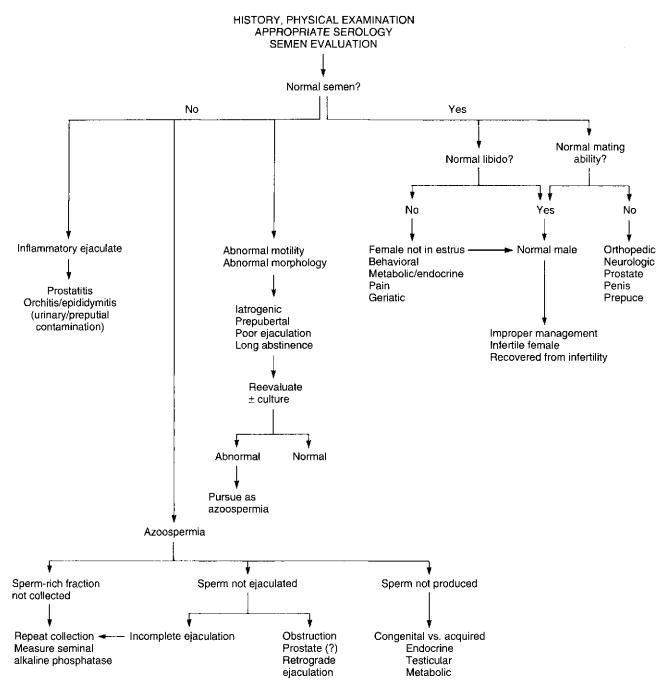


FIG 60-5 Diagnostic approach to male infertility.

din  $F_{2\alpha}$  should be used to maximize the number of sperm ejaculated (see p. 953). In cats another series of electrical stimulation should be given because the occasional azoospermic sample happens in normal males.

Spermatogenesis is a complex process that can be affected by environmental factors such as scrotal temperature; metabolic disorders, especially endocrinopathies; toxins and drugs; and infection. A thorough history taking and physical examination, ultrasound examination of the reproductive tract, semen culture, and standard laboratory tests help identify these possibilities. In addition, oligozoospermia and azoospermia may result from primary testicular failure or bilateral obstruction of the ductus deferens or epididymes. Because bilateral obstruction could occur at the level of the prostate gland, the prostate should be carefully evaluated. Measuring the seminal alkaline phosphatase activity (see p. 957) should help determine whether epididymal fluid was collected. High seminal alkaline phosphatase activity indicates that epididymal fluid, which should contain high numbers of motile sperm, was collected and that obstruction

to flow from the epididymes is apparently not the cause of the low sperm count.

Retrograde ejaculation of semen into the urinary bladder rather than out the urethra is another cause of oligozoospermia. This condition is thought to be neurogenic in origin, perhaps resulting from inadequate pressure in the proximal urethra or neck of the bladder. Some spermatozoa normally pass retrograde during ejaculation but substantially more do so during electroejaculation than during natural copulation. In the event of pathologic retrograde ejaculation, the volume of semen or the number of spermatozoa discharged is lower than normal. Retrograde ejaculation is diagnosed on the basis of finding excessive numbers of sperm in urine after ejaculation. Urine may be obtained by catheterization or cystocentesis. Some sperm are normally found in urine, but large numbers, especially approaching those in discharged semen, are considered abnormal. Treatment with α-adrenergic drugs (e.g., pseudoephedrine, 4 to 5 mg/kg, administered orally q8h or twice, 3 hours and 1 hour, before breeding) to increase urethral tone in dogs with retrograde ejaculation has been recommended, but experience with this treatment is limited.

The treatment of oligozoospermia and azoospermia depends on finding and eliminating the cause. Unfortunately, this is not always possible. Oligozoospermic males may be subfertile rather than infertile. It is assumed that sperm reserves and spermatogenesis are poor in oligozoospermic males; therefore they should be bred judiciously. This means allowing for adequate time between breedings so that sperm reserves can be replenished, performing insemination at the optimal time determined by ovulation timing, and breeding only to healthy, fertile females. Dogs with as few as  $20 \times 10^6$  to  $100 \times 10^6$  sperm per ejaculate have been reported to successfully impregnate normal, fertile bitches when ejaculation has been limited to twice, done at a 2-day interval. Intrauterine, rather than intravaginal, insemination may also be considered.

Oligozoospermia may or may not progress to azoospermia, depending on the cause. As a general rule, azoospermic males tend to remain azoospermic, especially if testicular size is abnormally small. The finding of small testes in an infertile male suggests the presence of congenital hypoplasia or acquired testicular atrophy or fibrosis, none of which is likely to be reversible. Because recovery from a testicular insult is slow and because canine spermatogenesis takes 62 days, the animal could reasonably be evaluated every 2 months for 6 to 12 months.

#### CONGENITAL INFERTILITY

Congenital causes of infertility should be considered in azoospermic animals that have no history of siring a litter or other reproductive activity. Abnormalities of the hypothalamic-pituitary-gonadal axis, such as hypogonadotropic hypogonadism; anatomic abnormalities of the Wolffian duct system, such as atresia; and disorders of sexual differentiation, such as intersex, are possible causes. Successfully correcting the congenital causes of infertility is unlikely. The diagnostic evaluation necessary to confirm a specific cause of congenital infertility can be quite extensive unless the external genitalia are abnormal or an infertile tomcat happens to have a calico or tortoiseshell coat color. The black and orange coat color each require an X chromosome to be expressed. Because male cats normally have only one X, they cannot express both coat colors. Therefore a male cat with calico or tortoiseshell color has either XXY or one of several reported chimeric states. Some of these cats are phenotypically normal males with normal spermatogenesis, presumably because of chimerism with the normal feline 38 XY karyotype in the gonadal tissue.

The phenotypic, gonadal, and chromosomal sex of the animal can be determined. The chromosomal sex can be determined by karyotyping. The phenotypic sex is determined by physical examination of the external genitalia. The internal genitalia (Müllerian and Wolffian duct derivatives) can be examined by ultrasonography, laparoscopy, or laparotomy. The gonadal sex can be assessed by endocrinologic evaluation (serum testosterone and LH concentrations) and gonadal biopsy. Otherwise, the diagnostic plan is the same as that for males with acquired infertility.

# ACQUIRED INFERTILITY

Animals with acquired infertility are known, or at least thought, to previously have had functionally and anatomically normal reproductive tracts. In some instances the onset of infertility or subfertility may be identified by a review of the breeding record, looking for a diminution in litter sizes and pregnancy/whelping rates. In other cases the time of onset of infertility is never determined. A thorough history should pay special attention to the possibility of toxin- or drug-induced infertility, excessive stress, or excessive frequency of ejaculation. A complete physical examination, semen evaluation and culture, ultrasonographic evaluation of the reproductive tract, and B. canis serology in dogs should be done. If these fail to establish the diagnosis, a thorough metabolic and endocrine evaluation should be done before more invasive procedures, such as testicular biopsy, are performed.

Bacterial infection of the testes, epididymides, or scrotum can cause alterations in spermatogenesis as a result of the destructive properties of the organisms themselves and as a result of local swelling and hyperthermia. *B. canis, Mycoplasma*, and herpes virus infections are discussed in Chapter 58. The role of bacterial prostatitis in canine infertility is unclear, but most theriogenologists consider bacterial prostatitis to be a common, potentially reversible cause of infertility. Appropriate antibiotic therapy should be initiated if the semen culture is positive for pathologic numbers of bacteria. Appropriate antimicrobial therapy should continue for a minimum of 2 to 4 weeks, or longer in the case of chronic bacterial prostatitis.

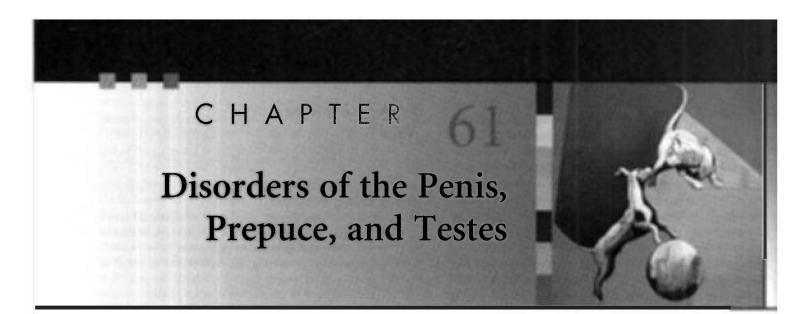
A variety of pharmaceutical agents have been empirically used to enhance semen quality in many species. The effect of drugs and nutriceuticals on the spermiogram depends on the cause of the problem. As discussed earlier, prostaglandin  $F_{2\alpha}$  has been shown to increase the number of sperm ejaculated and the ease with which semen is collected from normal dogs. In oligozoospermic and azoospermic dogs with pathologically high serum concentrations of estradiol and low serum concentrations of testosterone, treatment with an aromatase inhibitor corrected the hormonal concentrations and improved semen quality, although not to expected normal values. Treatment with vitamin E improved the spermiogram in dogs being given dexamethasone, presumably by protecting against oxidative stress. Whether vitamin E would improve semen quality in otherwise normal animals is not known because studies in rabbit, ram, and boar have yielded conflicting results.

There are anecdotal reports that treatment with GnRH or prolactin improved semen quality in dogs with abnormal spermiograms, but these reports lack evidence of the underlying pathophysiology, such as GnRH or gonadotropin deficiency or hyperprolactinemia. Glycosaminoglycans, omega-3 fatty acids, and vitamin C have also been tried. A dietary supplement containing docosahexaenoic acid (DHA), vitamin E, and selenium (PROSPERM®, Minitube America) has been used to improve semen quality in stallions and boars. Another antioxidant supplement (CellAdvance®, Vetri-Science Products) and a carnitine supplement (Motility Plus®, Platinum Performance) are also available. With few exceptions, there is not yet evidence of efficacy of these products in the treatment of canine infertility. Were these to be used, the duration of treatment would probably be at least 4 to 8 weeks because the canine spermatogenic cycle is about 60 days.

Testicular aspiration or biopsy should be considered when the abnormalities in the spermiogram have not improved after several months, especially in animals with normal testicular size. Testicular biopsy may be unwarranted in animals with testes that are already substantially smaller than normal because the testicular degeneration, atrophy, or fibrosis that cause small testicles are usually considered irreversible. Testicular biopsy specimens from cats older than 7 years show diminished spermatogenesis and degeneration of seminiferous tubules compared with the findings in younger cats. These are considered typical age-related changes. Testicular atrophy is common in dogs older than 10 years. A portion of the biopsy specimen should also be submitted for bacterial culture. The following histologic lesions have been identified in dog testes: neoplasia, suppurative and nonsuppurative inflammation, mycotic orchitis, lymphocytic orchitis, granulomatous orchitis, spermatogenic arrest, and testicular degeneration. There is limited information available on cats other than information on the testicular changes associated with aging.

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# CHAPTER OUTLINE

#### PENILE DISORDERS

Penile Trauma

Priapism

Miscellaneous Penile Disorders

Persistent Penile Frenulum

# PREPUTIAL DISORDERS

Balanoposthitis

**Paraphimosis** 

Phimosis

#### **TESTICULAR DISORDERS**

Cryptorchidism

Testicular neoplasia

Orchitis and Epididymitis

Torsion of the Spermatic Cord

Miscellaneous Testicular and Scrotal Disorders

#### PENILE DISORDERS

#### PENILE TRAUMA

Traumatic injury of the penis occurs in dogs and cats as a result of fighting, being hit by cars, mating inappropriately, and jumping through or upon, rather than over, barriers. Hematomas, lacerations (Fig. 61-1), and fracture of the os penis are injuries that may occur. Penile injuries are usually painful. Other clinical signs include swelling, bruising, and hemorrhage. The prepuce may or may not be similarly affected, depending on whether the penis was extruded (as it would be if erect) when the injury occurred. The diagnosis is made by visual examination of the penis and radiographic examination of the penile urethra and os penis. The integrity of the urethra should be evaluated by retrograde urethrography whenever significant penile trauma is identified. Ultrasonography and color-flow Doppler may help differentiate penile hematoma from priapism.

Treatment includes cleansing of the wounds and debridement if necessary. Lacerations may require surgical closure using absorbable sutures. An antibiotic cream should be

applied to the surface of the penis, and the penis should be protruded from the prepuce twice daily until the lesions are healed. This is done to prevent adhesions between the penis and the prepuce from forming. Sexual arousal and other types of excitement must be avoided until the penile lesion is completely healed because erection before then is likely to result in hemorrhage and possibly dehiscence.

Fractures of the canine os penis are very uncommon but are often associated with a urinary outflow tract obstruction or a urethral tear. In addition to the local signs associated with the trauma, these animals may have signs referable to a distended urinary bladder or postrenal uremia. The treatment adopted depends on the severity of the urethral damage and fracture displacement. As an emergency treatment, the urinary bladder may be decompressed by cystocentesis. An indwelling urethral catheter may be placed while the urethra heals. Urethral tears should be sutured if necessary. Urethrotomy or urethrostomy could be considered in some circumstances to temporarily or permanently divert urine flow. Systemic antibiotics should be administered to prevent urinary tract infection. Displaced fractures of the os penis can be immobilized with orthopedic wires. Immobilization is not required in animals with fractures that are not displaced because the penis itself provides adequate support. Occasionally, calluses that form during the healing of the os penis obstruct the urethra. It may be necessary to amputate the penis in the event of severe penile trauma.

#### **PRIAPISM**

Priapism is abnormal, persistent erection that is not associated with sexual arousal. The neurophysiology of erection includes sympathetic innervation via the hypogastric nerve, parasympathetic innervation via the pelvic nerve, and somatic and sensory input via the pudendal nerve. Parasympathetic innervation is considered to be responsible for stimulating erection, and sympathetic innervation is considered to be responsible for stimulating ejaculation. During the normal process of erection, relaxation of sinusoidal smooth muscle and increased flow through the arteries and arterioles facilitate rapid filling of the sinusoidal system, which in turn compresses the venous channels and occludes



FIG 61-1 Penile laceration in a Maltese.

outflow. During the process of detumescence, the trabecular smooth muscle contracts, enabling the venous channels to reopen, and the trapped blood is expelled.

Spinal cord lesions, general anesthesia, phenothiazine administration, and thromboembolism are reported causes of priapism. Venous occlusion at the base of the penis, due to any cause, could result in priapism. In many cases the cause of priapism is undetermined, but the outcome is occlusion of venous outflow and stagnation of blood that will eventually clot in the cavernous sinuses. In addition, ischemic necrosis is common. Fortunately, priapism occurs rarely in dogs and cats.

Some high-strung dogs transiently develop erections when they are excited for any reason. This is not priapism. These transient erections in highly excitable dogs usually diminish as the dog matures. If not, castration, with or without behavioral modification, is usually curative. Priapism is also different from the erection that occasionally persists in some dogs for longer than expected after copulation or semen collection. In these cases, if the estrous bitch is still present, she should be removed from the premises. The male dog should be taken out of the room in which copulation or semen collection took place. These distractions are often sufficient and the erection subsides. If not, sedation or application of cold water compresses could be considered. Priapism should also be differentiated from other causes of penile swelling, such as hematoma or edema. Penile hematomas usually form as a result of trauma or bleeding disorders. Edema usually occurs as a result of paraphimosis. Simple visual inspection and palpation of the penis are usually sufficient to differentiate the conditions. An ultrasound and/or color-flow Doppler examination may help differentiate hematoma from priapism.

During priapism clotting of the blood trapped in the cavernous sinuses, ischemia, and necrosis develop quickly. Therefore pharmacologic intervention, if it is to be successful, must be done within hours. Nonischemic priapism may respond to pharmacologic treatment with anticholinergic or antihistaminic agents, such as diphenhydramine and benztropine. Benztropine contains the active ingredients of atropine and diphenhydramine; a dose of 0.015 mg/kg intravenously has been suggested for dogs. The  $\beta$ -adrenergic



FIG 61-2 Priapism and paraphimosis in a German Shepherd Dog.

agonist terbutaline has also been used successfully in the treatment of priapism in men. Surgical drainage and intracorporeal lavage have also been reported as successful treatments. Unfortunately, many of the reported cases in dogs and cats were not presented to veterinarians until the condition had been present for days to weeks, by which time necrosis necessitated penile amputation or perineal urethrostomy.

During priapism (Fig. 61-2) the penis should be protected against additional damage or irritation that may perpetuate the problem or invite the development of sequelae, such as edema, thrombosis, fibrosis, penile paralysis, or necrosis. Physical treatments include cleansing the penis, applying antibiotic cream, and attempting to maintain the penis within the prepuce until the condition subsides.

#### MISCELLANEOUS PENILE DISORDERS

Vesicles, ulcers, pyogranulomatous lesions, warts, and neoplasia of the penis have been identified in dogs. The clinical signs are similar and include a preputial discharge, excessive licking of the prepuce or penis, or a mass protruding from the prepuce. These lesions are differentiated by visual examination, exfoliative cytologic studies, bacterial and fungal cultures, and biopsy. Transmissible venereal tumor (TVT) is the most commonly reported penile tumor in dogs (see Chapter 57). The macroscopic appearance of TVT and penile warts may be similar. In our experience, penile warts often resolve spontaneously after biopsy of the lesion (Fig. 61-3). The cause of vesicular lesions is uncertain. Canine herpes virus has been implicated but is usually not documented. Herpes virus infection is discussed in Chapter 58. Hyperplasia of the lymphoid follicles at the base of the penis may have a similar appearance to vesicles. Lymphoid follicular hyperplasia is thought to develop as a result of chronic irritation. Ulcers and pyogranulomatous lesions are uncommon, but when present they seem to be associated with infection and balanoposthitis.

Congenital penile disorders other than a persistent penile frenulum are rare. Penile hypoplasia has been noted in dogs and cats. Some affected animals have had an abnormal complement of sex chromosomes. In most the penile hypoplasia has been an incidental finding. In one dog it was associated with urine pooling in the preputial cavity. Diphallia, or duplication of the penis, has been reported in dogs and cats. Hypospadia is an anomaly in closure of the urethra that occurs because of a defect in the androgen



FIG 61-3
Penile warts in a geriatric Dachshund.



FIG 61-4
Hypospadia involving the urethra, penis, prepuce, and scrotum of an English Bulldog pup.

receptor(s). The result is one or more abnormal openings into the urethra anywhere along its length. The penis, prepuce, and sometimes the scrotum are simultaneously and similarly affected (Fig. 61-4). Hypospadia has been reported more often in dogs than in cats. Besides the abnormal appearance of the external genitalia, clinical signs include urinary incontinence and urinary tract infection. Affected animals may have additional congenital anomalies, such as cryptorchidism. Surgical correction may be considered.

## PERSISTENT PENILE FRENULUM

Under the influence of androgens, the surfaces of the glans penis and the preputial mucosa normally separate before or within months of birth, depending on the species of animal. If this separation does not occur, connective tissue persists between the penis and the prepuce. In dogs the persistent penile frenulum is usually located on the ventral midline of the penis (see Fig. 61-5). A persistent penile frenulum may cause no clinical signs, or it may be associated with preputial discharge or excessive licking of the prepuce. Persistent frenulum may cause the penis to deviate ventrally or laterally so that the dog is unable or unwilling to mate. The diagnosis is made by visual examination. Treatment is surgical excision, which can often be done using sedation with local anesthesia because the frenulum tends to be a sheer, avascular membrane.

Persistence of the adhesions of the prepuce and penis has been seen in male cats that are castrated between 7 weeks and 5 months of age, but the prevalence of this condition in the general cat population, irrespective of neuter status or age at castration, is unknown. Failure of the glans penis and preputial mucosa to separate prevents the penis from being fully extruded or causes deviation of the erect penis (see Fig. 61-5). The clinical significance, if any, of the failed penile-preputial separation seen in some cats neutered at very young ages remains to be determined.



A, Persistent frenulum in a dog. B, Failure of complete separation of the penile and preputial mucosa in a cat.

# BALANOPOSTHITIS

Inflammation or infection of the preputial cavity and penis, balanoposthitis, is very common in dogs and rare in cats. The offending organisms are usually members of the normal preputial flora (see Box 60-1), although infection with canine herpes virus and Blastomyces has also been reported. Balanoposthitis usually causes no clinical signs other than a purulent preputial discharge that is quite variable, from a scant white smegma to a copious green pus. The discharge associated with balanoposthitis is not sanguineous unless the cause is neoplasia or foreign material. The diagnosis of balanoposthitis is made by physical examination of the penis and preputial cavity all the way to the fornix, in a search for foreign material, neoplasia, ulceration, or inflammatory nodules. Cultures and cytologic studies are rarely performed, unless herpes virus or fungal infection is suspected because of the vesicular appearance of the lesions or the presence of similar lesions elsewhere on the body. The treatment of balanoposthitis is usually conservative. The hair should be clipped from the preputial orifice and from the surrounding area if discharge has been accumulating there. Flushing the preputial cavity with antiseptic solutions (e.g., chlorhexidine, povidone-iodine) seems to be helpful. Topical antibacterial medications may be instilled into the preputial cavity. Castration usually results in diminished preputial secretions. In persistent or refractory cases, cytology, culture, and endoscopic examination should be considered.

#### **PARAPHIMOSIS**

Paraphimosis is a condition in which the penis is prevented from retracting back into the preputial cavity. It occurs most frequently after an erection in dogs. Therefore it is seen quite often after semen collection and occasionally after copulation. Paraphimosis may occur in longhaired cats when the penis becomes entangled in the preputial hairs. Otherwise, it is uncommon in cats. The protruded penis usually becomes trapped because the prepuce has turned in on itself (see Fig. 61-2). Presumably, this occurs because the skin or hair at the preputial orifice adheres to the surface of the penis and is pulled into the preputial cavity as an erection subsides. The inverted preputial skin then compromises the circulation to the protruded penis.

The signs of paraphimosis depend primarily on its duration. Initially, the exposed penis is normal in appearance and nonpainful. However, after several minutes the exposed penis becomes edematous (see Fig. 61-6) and increasingly painful. In addition to the damage caused by continued poor circulation, the exposed penis is subject to trauma. The surface becomes dry, and fissures may develop. The urethra is usually not damaged. The unexposed penis and the uninvolved prepuce are normal and nonpainful. Long-standing paraphimosis may result in gangrene or necrosis.

Paraphimosis is diagnosed by visual inspection. The exposed penis may have become so painful that sedation or anesthesia is required, although this is not usually necessary



FIG 61-6
Correction of paraphimosis. Note edematous tip of penis.

early on. Treatment involves returning the prepuce to its normal configuration, restoring circulation to the penis, and replacing the penis in the preputial cavity. This is accomplished by gently sliding the prepuce in a posterior direction, such that more of the glans penis is protruded. The prepuce is thus retracted until the cranial aspect of the prepuce "unfolds" and the preputial orifice is exposed (see Fig. 61-6). Circulation to the penis usually improves immediately after the prepuce is restored to its normal configuration. Penile edema then begins to subside. The surface of the penis is cleansed or debrided as necessary. Topical antibiotic or an antibiotic-steroid cream may be applied if the penile mucosa has been damaged. Even though some penile edema may still be present, the prepuce usually slides easily over it and the penis is thus replaced in the preputial cavity. Water-soluble lubricant should be applied as necessary to accomplish this. If, even after circulation is restored, the edematous tissue is of sufficient magnitude that the prepuce cannot slide over it, application of pressure with a cool water compress is usually effective in resolving the edema.

Rarely is it necessary to enlarge the preputial orifice. If it is, an incision is made on the ventral midline of the prepuce, and after the penis is in place, the incision is closed in separate layers. The penis will usually stay within the preputial cavity, and penile swelling quickly subsides. The degree of swelling can be assessed by palpating the penis through the prepuce if there is concern that protruding the penis from the preputial cavity will be unduly painful. Rarely does the still-swollen penis protrude from the prepuce. The preputial orifice may be temporarily (1 to 24 hours) sutured closed, but there is the risk that urine will accumulate in the preputial cavity during this time. If the penis has become necrotic or gangrenous, penile amputation is indicated.

Conditions other than paraphimosis may also cause the penis to protrude from the prepuce. These include priapism, phimosis, an abnormally short prepuce in dogs, and a ring of preputial hair in cats. Penile trauma may cause penile hematomas to form. The swelling associated with the extravasation of blood may be sufficiently severe to cause the penis to protrude. Treatment is conservative and consists in

protecting the exposed penis from trauma. The preputial orifice may also be temporarily closed. If possible, the hematoma is allowed to resolve spontaneously; otherwise, it can be drained surgically. Foreign material within the preputial cavity or around the glans penis may also cause the penis to protrude.

#### **PHIMOSIS**

Phimosis is a condition in which the penis is trapped within the preputial cavity. It usually occurs as a congenital defect in which the preputial opening is abnormally small and the penis cannot protrude. Phimosis is uncommon in cats and dogs. It may be recognized in young animals as a cause of a urinary outflow tract obstruction or of the dribbling of urine that has accumulated in the preputial cavity. Phimosis may be recognized in an affected male when it is unable to copulate. It is treated by surgically enlarging the preputial orifice. The preputial hairs of longhaired cats may entangle the preputial orifice, causing clinical signs similar to phimosis. It is treated by clipping the preputial hairs.

## **TESTICULAR DISORDERS**

#### CRYPTORCHIDISM

Cryptorchidism is the failure of one or both testes to descend into the scrotum. The condition may be unilateral or bilateral. The undescended or retained testicle may be located in the abdominal cavity, in the inguinal canal, or in the subcutaneous tissue between the external inguinal ring and the scrotum. On rare occasions a cryptorchid testis is found in the perineal subcutis dorsal or lateral to the scrotum. The testicular hormone insulin-like factor 3 (also called relaxinlike factor), which is produced by prenatal and postnatal Leydig cells, mediates the transabdominal testicular descent from the caudal pole of the kidney to the inguinal canal. It induces growth and differentiation of the gubernaculum from the caudal suspensory ligament. The transabdominal migration of the fetal testis is independent of androgens, whereas the inguino-scrotal descent is mediated by testosterone. Testosterone causes regression of the cranial suspensory ligament. During the inguino-scrotal phase of migration, there is shortening of the gubernaculum and eversion of the cremaster muscle. The normal time of testicular descent has not been firmly established in dogs or cats. In cats testicular descent appears to be a prenatal event. In dogs testicular descent is complete by 10 to 42 days of age. Although later descent is possible, a diagnosis of cryptorchidism is likely if the testes are not palpable within the scrotum by 8 to 10 weeks of age. Because the testes are so small and mobile in infant animals, some veterinarians have recommended that a diagnosis of cryptorchidism not be made until a dog is 6 months old.

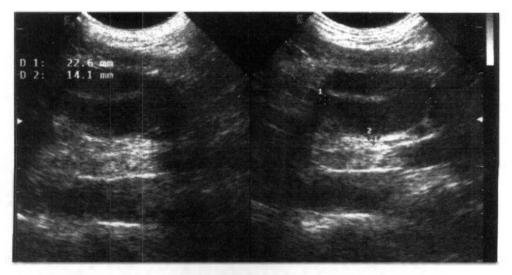
Unilateral cryptorchidism is more common than bilateral cryptorchidism in both dogs and cats. The undescended testis is found in the abdomen or in the subcutaneous tissues in the inguinal area with about equal frequency. Bilaterally

undescended testes are most often found in the abdomen. There is no apparent difference in the prevalence of right- or left-sided unilateral cryptorchidism in dogs or cats. True monorchidism (congenital absence of one testis) is extremely rare. The incidence of cryptorchidism in the general animal population is unknown. Of 1345 cats presented for castration, 23 (1.7%) were cryptorchid, which is similar to the findings in 3038 feral cats trapped for neutering, of which 35 (1.2%) were cryptorchid and 46 (1.5%) were thought to have been previously castrated. The prevalence of cryptorchidism in dogs in various hospital populations is reported between 1.2% and 5%. Cryptorchidism was found in 44 (2.6%) of 1679 dogs from a pet store.

Although the specific mode(s) of inheritance is not known in either species, cryptorchidism is generally believed to be associated with family lineage. Therefore the prevalence is likely to vary with breed and species. For example, the incidence of cryptorchidism in 2929 boxers was 10.7% (Nielen et al., 2001). The simplest model consistent with the evidence available is a sex-limited, autosomal recessive mode of inheritance. The expression of the trait is limited to males, but the genetic defect is not linked to the sex chromosomes. Therefore both males and females carry the gene and can pass it on to their offspring, but only the homozygous males are phenotypically abnormal (cryptorchid) and readily identifiable. Females cannot express the trait regardless of their genotype. Heterozygous (carrier) males have normal phenotype; in other words, they are not cryptorchid. Therefore, with the exception of a homozygous × homozygous cross, which would produce cryptorchid male puppies, some litters are likely to contain all phenotypically normal males, whereas other litters from the same dam and sire will have affected males. However, the inheritance of cryptorchidism is known to be more complex than that explained by the simple autosomal recessive, sex-limited model, providing yet another possible explanation for why each litter from the same breeding pair does not always have the same phenotypic result.

The undescended testis is not normal, Spermatogenesis is usually completely absent, especially in intraabdominal testes, because of the higher temperature. Spermatogenesis does not fully recover, even if the testis descends into the scrotum at a later time. Because interstitial cells continue to produce testosterone, libido and secondary sex characteristics are normal. Bilaterally cryptorchid animals are sterile, which effectively removes them from the gene pool. Although the number of spermatozoa in the ejaculate of animals with unilateral cryptorchidism is less than that of normal animals, they are expected to be fertile. Therefore unilaterally cryptorchid males will perpetuate the trait if allowed to breed.

There is no known medical treatment that can reliably cause cryptorchid testes to descend. Favorable results occasionally have been noted in male dogs and in boys treated with human chorionic gonadotropin. However, it is generally believed that the apparent success is actually the result of the coincidental spontaneous descent of mobile testes that were located very near the scrotum. There appear to be no reports of the successful medical management of intra-



**FIG 61-7**Sonogram showing an intraabdominal cryptorchid testis in a dog. (Courtesy Dr. Gustavo Sepulveda, East Lansing, Mich.)

abdominal cryptorchidism in any species. Castration of cryptorchid dogs is recommended primarily because of the increased risk of testicular neoplasia in retained testes. Ultrasonography may be helpful in locating the retained testis (Fig. 61-7).

In dogs testicular neoplasia is as much as 13 times more likely to develop in undescended than in descended testes. Because testicular neoplasia, even in scrotal testes, is so common in older dogs, this represents a significant risk. Castration of cryptorchid dogs while they are young is therefore recommended. Sometimes the cryptorchid testis is difficult to find. If, at the time of surgery, the ductus deferens, testicular vessels, or epididymis are found, it is highly likely that the ipsilateral testis also exists. True monorchidism is extremely rare. After unilateral castration, suspected monorchidism should be confirmed with appropriate hormonal testing, such as determining serum testosterone concentrations before and after gonadotropin releasing hormone (GnRH) or measuring serum luteinizing hormone (LH) concentrations. Testicular neoplasia is also more common in cryptorchid testes in men. Even after orchiopexy, the standard treatment for cryptorchidism in people, the previously ectopic testis is at greater risk for testicular cancer than the descended testis. The risk of testicular cancer in cryptorchid men treated with orchiopexy after puberty (age 13 years) is approximately twice that of men treated before the age of 13. Testicular neoplasia is rare in cats, although it has been reported in cryptorchid testes.

#### **TESTICULAR NEOPLASIA**

Testicular tumors are very common in dogs older than 10 years of age, second only to skin tumors. In most dogs testicular tumors are found incidentally during physical examination, castration, or necropsy. Testicular tumors are rare in cats. In dogs Sertoli cell tumors, Leydig cell (interstitial cell) tumors, and seminomas occur with about equal frequency



BOX 61-1

Paraneoplastic Syndromes Associated with Hyperestrogenism

Alopecia

Pigmentation

Feminization of males: gynecomastia, pendulous scrotum,

and prepuce

Squamous metaplasia of the prostate

Bone marrow suppression: anemia, thrombocytopenia, leu-

kopenia

Depressed spermatogenesis

Testicular atrophy

except in intraabdominal testes, in which the most common neoplasm is Sertoli cell tumor. The most important risk factors for testicular neoplasia are age and cryptorchidism. Testicular tumors are rare in dogs younger than 6 years of age. Testicular cancer is diagnosed almost 11 times more often in cryptorchid testes than in scrotal testes. Certain gene expressions and carcinogens are also risk factors.

# **Diagnosis**

The most common clinical sign of testicular neoplasia is enlargement of the testis. Sertoli cell and interstitial (Leydig) cell tumors can produce hormones, particularly estrogen, that cause paraneoplastic syndromes. These include atrophy of the contralateral testis, bone marrow suppression, pendulous prepuce, gynecomastia, alopecia and hyperpigmentation, and squamous metaplasia of the prostate (Box 61-1). The gynecomastia and pendulous prepuce have been referred to as *feminization*. The bone marrow suppression induced by estrogen is characterized by anemia, thrombocytopenia, and/or leukopenia. Some of the clinical signs may be related to anemia or bleeding as a result of the thrombocytopenia.

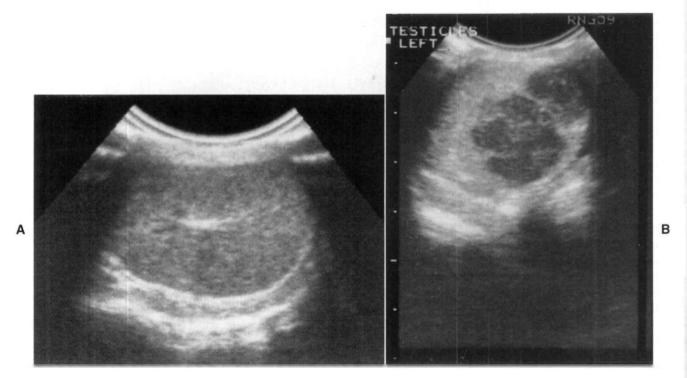


FIG 61-8
Sonogram of normal right testis (A) and left testis (B) with a seminoma in an infertile, 9-year-old English Bulldog. After hemicastration the dog sired a litter of nine pups. Hatch marks are 1 cm.

Intraabdominal testicular tumors of sufficient size may cause interference with other abdominal organs. Uncommonly, dogs with testicular tumors may be presented because of infertility, but most affected animals are past their breeding years.

The diagnosis of testicular neoplasia is usually straightforward. It should be suspected as a possible cause for any testicular mass and also feminization. The index of suspicion is highest in old, cryptorchid males. The diagnosis is most challenging in dogs that do not have scrotal testes because they may erroneously be assumed to have previously been castrated. Exfoliative cytology of the preputial mucosa may confirm the presence of excessive estrogen, which causes it to cornify like the vaginal epithelium (see Chapter 56). A testicular tumor is by far the most likely source of hyperestrogenism in a male dog, although pathologic production of sex hormones by the adrenal gland has been reported in dogs with hyperadrenocorticism. Ultrasonography is helpful in evaluating the testes of animals in which testicular neoplasia is suspected but not palpable. They have a variable echo texture. Tumors less than 3 cm in diameter are usually hypoechoic (Fig. 61-8). The larger tumors tend to disrupt normal testicular architecture and may contain focal areas of ischemic necrosis; thus large testicular tumors usually have mixed echogenicity. Ultrasonography and radiology can be used to evaluate intraabdominal testes, but testes similar in size to the diameter of the small bowel may be difficult to identify.

Fine-needle aspiration of palpable testicular masses is easily performed, but it is rarely done when the index of suspicion of neoplasia is high because tissue specimens can be obtained at the time of castration. Nevertheless, cytologic examination of aspirated material can be very helpful in differentiating a testicular neoplasm from other masses, such as abscess or granuloma, or if owners are reluctant to consider castration without a definitive diagnosis. A complete blood count is indicated to assess the possibility of bone marrow toxicity. Because most affected dogs are geriatric, a preoperative biochemical panel and urinalysis are also reasonable.

Treatment for testicular tumors is castration. If the dog has value as a stud, unilateral castration could be performed. The clinical signs associated with hyperestrogenism usually resolve promptly, except for bone marrow toxicity and infertility. The latter is not surprising, given the age of most affected dogs. The testis should always be submitted for histopathologic evaluation. Because most canine testicular tumors are benign, it would be reasonable to delay complete staging of the tumor until histopathologic confirmation of malignancy. Intraabdominal metastasis is more common than pulmonary. Treatment options for malignant and metastatic testicular tumors should be considered in consultation with a veterinary oncologist.

#### ORCHITIS AND EPIDIDYMITIS

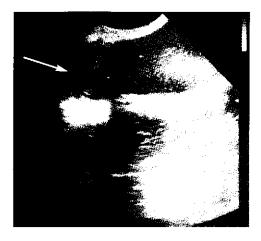
The testis or epididymis can become infected via the hematogenous route, through the ascension of pathogens from

elsewhere in the urogenital tract, or as a result of penetrating wounds. Extension or progression of infection from the epididymis to the testis, or vice versa, is common. Orchitis-epididymitis is more common in dogs than in cats. Aerobic bacteria are most often implicated. *Mycoplasma, Brucella canis* (see Chapter 58), *Blastomyces, Ehrlichia,* Rocky Mountain spotted fever, and feline infectious peritonitis are also reported to infect the testes, epididymides, or scrotum. Bacterial infection of the testes, epididymides, or scrotum causes alterations in spermatogenesis as a result of the destructive properties of the organisms themselves and as a result of local swelling, inflammation, and hyperthermia.

The clinical signs of orchitis-epididymitis vary with the chronicity of the infection. Acute infections are usually associated with swelling of the scrotum and scrotal contents and are painful. The affected epididymis or testis is enlarged, firm, and warm. The scrotal skin may be inflamed, and dogs may lick the scrotum excessively. Fever and lethargy may be present in animals with systemic infections. Conversely, some affected animals may show minimal discomfort, and the owner may not notice the acute phase. The scrotum is usually normal in animals with chronic orchitis-epididymitis. Eventually, the testis becomes soft and atrophic. Then the epididymis may seem more firm and prominent than usual. Infertility is common in animals with either acute or chronic orchitis-epididymitis, and it may be the presenting complaint.

#### Diagnosis

Orchitis-epididymitis is diagnosed on the basis of physical examination, ultrasonography (Fig. 61-9), cytology, and culture findings. Specimens for culture and cytology may be obtained by collection of semen or fine-needle aspiration of the testis. Semen from dogs with active orchitis-epididymitis contains many inflammatory cells (leukospermia) and abnormal spermatozoa. Bacteria or other infectious agents, however, are usually not seen during cytologic evaluation of



Sonogram of abnormal canine epididymis (arrow) typical of suppurative epididymitis. Normal-appearing testis is to the right.

semen. They are more commonly observed in specimens obtained by fine-needle aspiration. In animals with chronic infection and atrophy of the testes, the number of inflammatory cells and spermatozoa decreases, eventually resulting in azoospermia. Serologic tests for *B. canis* should always be performed in dogs with these clinical and cytologic findings. A thorough evaluation of the prostate gland is also warranted.

Semen cultures in dogs with active bacterial orchitisepididymitis usually yield more than 105 colony-forming units/ml of semen. However, culture results must be interpreted in light of the normal urethral florae and other clinical and cytologic findings (see Chapter 60). Microbiologic cultures may be negative in animals with chronic orchitisepididymitis. This is frequently the case in animals with chronic B. canis infection. Therefore negative culture results do not necessarily exclude infection as the inciting cause. The results of cytologic and microbiologic evaluation of semen from dogs with orchitis-epididymitis are indistinguishable from those of prostatitis. Further, prostatitis and orchitis-epididymitis may be concurrent. Therefore the prostate should always be thoroughly evaluated by palpation, ultrasonography, and cytologic evaluation of the third fraction of the ejaculate or specimens obtained by fine-needle aspiration of the prostate.

#### Treatment

Appropriate antimicrobial therapy should be initiated on the basis of culture results. Antibiotics to consider pending results of sensitivity testing are those that are usually effective against the common urogenital organisms. These antibiotics include enrofloxacin, amoxicillin, clavulanate-amoxicillin, chloramphenicol, and trimethoprim-sulfonamide, which are effective against either gram-negative or gram-positive organisms. Cephalosporins and tetracycline can also be considered. Antimicrobial therapy, determined on the basis of the results of culture and sensitivity testing, should continue for a minimum of 2 weeks. Soaking the scrotum in cool water may help to minimize the damage caused by hyperthermia and swelling. In cases of unilateral involvement, unilateral orchiectomy may be the best way to protect the apparently unaffected gonad. Antibiotics should be administered regardless of whether surgery is performed. The prognosis for recovery of fertility is poor in dogs or cats with orchitis and epididymitis, regardless of the causative organism. Orchiectomy effectively decreases the burden of infection and should be considered if fertility appears to be irreversibly lost.

# TORSION OF THE SPERMATIC CORD

Torsion of the spermatic cord is often called *testicular torsion*. Torsion of the spermatic cord occurs more often in intraabdominal testes than scrotal testes (Fig. 61-10). The clinical signs are related to the acute abdominal pain that results. If torsion of a scrotal testis occurs, pain is also the major clinical sign. There is also scrotal and testicular swelling, which can be quite pronounced. Often, the thickened spermatic

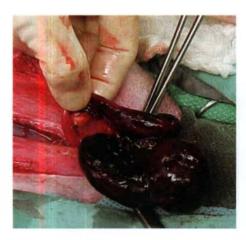


FIG 61-10 Spermatic cord torsion of an abdominal cryptorchid testicle in a dog.

cord can be palpated. Ultrasonographic examination of the affected testis and spermatic cord usually reveals the spiral course of the spermatic vessels. Treatment is unilateral orchiectomy because spermatogenesis is irreparably damaged as a result of ischemia within 1 to 2 hours of testicular torsion. Although some recovery is possible, fibrosis usually occurs.

# MISCELLANEOUS TESTICULAR AND SCROTAL DISORDERS

Whenever a lesion is found in one testis, both testes should be thoroughly evaluated. Differentiating focal lesions such as tumors, granulomas, spermatoceles or cysts can be accomplished with ultrasound and fine-needle aspiration. Spermatoceles are caused by stasis and accumulation of sperm. They occur more commonly in the ductus deferens or epididymal ducts than in the seminiferous tubules. They may be congenital or acquired as a result of trauma, including fine-needle aspiration or biopsy. They may be the result, or the cause, of local inflammation and the development of sperm granulomas. They may also be incidental findings. Cysts may arise in the seminiferous tubules or the rete testis. They are usually incidental findings during ultrasound, but, like spermatoceles, they may cause a mass or obstruction to the flow of sperm.

People often assume that an enlarged scrotum is due to testicular enlargement. Other causes of scrotal enlargement include epididymal or spermatic cord enlargement (e.g., scirrhous cord), herniation of omentum or small bowel into the scrotum, scrotal edema, or hydrocele. Hydrocele is the accumulation of fluid between the visceral and parietal

tunics of the scrotum. It may be a transudate, hemorrhage, or exudate. To differentiate among these causes, careful palpation and ultrasound of the scrotal contents are necessary. The scrotal skin is susceptible to contact irritant dermatitis. Self-mutilation of the scrotal skin sometimes occurs as a result of underlying gonadal disease. Otherwise, the considerations for problems with the scrotal skin are the same as for skin elsewhere on the body.

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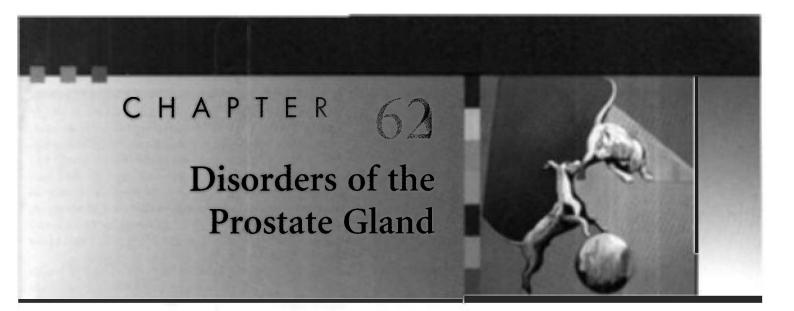
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# CHAPTER OUTLINE

OVERVIEW OF PROSTATIC DISEASE
DIAGNOSTIC EVALUATION OF THE PROSTATE
GLAND
BENIGN PROSTATIC HYPERPLASIA
SQUAMOUS METAPLASIA OF THE PROSTATE
ACUTE BACTERIAL PROSTATITIS AND PROSTATIC
ABSCESS
CHRONIC BACTERIAL PROSTATITIS
PARAPROSTATIC CYSTS
PROSTATIC NEOPLASIA

# **OVERVIEW OF PROSTATIC DISEASE**

Disorders of the prostate gland are common in dogs but very rare in cats. They include benign prostatic hyperplasia, squamous metaplasia, bacterial prostatitis, prostatic abscess, prostatic and paraprostatic cysts, and prostatic neoplasia. Clinical signs of prostatic diseases are similar because each causes some degree of prostatic enlargement or inflammation (Box 62-1). The most common clinical signs include tenesmus, blood dripping from the urethra independent of urination, and recurrent urinary tract infections. Blood is usually found in the urine and semen from dogs with prostatic disease. Additional, nonspecific signs, such as fever, malaise, and caudal abdominal pain, are often present in dogs with bacterial infections and neoplasia of the prostate gland. Prostatic adenocarcinoma may cause an animal's gait to be abnormal as a result of pelvic and lumbar vertebral metastatic lesions. Less commonly, prostatic diseases may cause urethral obstruction, infertility, or urinary incontinence.

# DIAGNOSTIC EVALUATION OF THE PROSTATE GLAND

A complete physical examination is performed. Palpation is done to assess the size, shape, symmetry, and consistency of

the prostate as well as to detect any discomfort. This is accomplished by both abdominal and rectal palpation. The enlarged prostate is rarely located completely within the pelvic canal. There is a positive correlation between prostatic size and age and also body weight. The clinical signs and physical findings will usually localize the disease process to the prostate gland, but they are not able to differentiate among the various prostatic conditions.

Diagnostic imaging, prostatic cytologic studies, bacterial culture, biopsy, or a combination of these studies is usually required to differentiate the specific prostatic disorders. Culture results from normal prostatic fluid should yield less than 100 colony forming units (CFUs)/ml. Abdominal radiographs help define the size, shape, and position of the prostate. Prostatic length of greater than 70% of the distance from the sacral promontory to the pelvic brim on the lateral abdominal radiograph is indicative of prostatomegaly. The radiographic appearance of the sublumbar lymph nodes, lumbar vertebrae, and bony pelvis should be examined for evidence of metastasis. A positive-contrast cystourethrogram can be performed if it is difficult to differentiate an abnormal prostate from the urinary bladder and to assess the prostatic urethra. Ultrasonography provides additional information about the homogeneity of the prostatic parenchyma, the urethral diameter, and the diffuse or focal nature of the disease (Fig. 62-2). The finding of urethral invasion or destruction during diagnostic imaging is highly suggestive of prostatic neoplasia. As can be seen from the similarities of the figures in this chapter, radiographic and ultrasonographic findings do not differentiate cysts from abscesses or hyperplasia from metaplasia, prostatitis, or diffuse neoplasia.

Prostatic material for cytologic and microbiologic examination can be obtained by several methods. The rationale for prostatic massage or brush techniques is that material from the prostate may be recovered via the urethra. The accuracy of the results will depend on whether the prostatic lesion communicates in some way with the urethra. Prostatic massage is performed by placing a urethral catheter and removing urine from the bladder. An aliquot of urine is saved for future comparison. The catheter is then withdrawn

# BOX 62-1

## Clinical Signs of Prostatic Disease

#### **Common Signs**

Blood dripping from urethra without micturition Tenesmus Recurrent urinary tract infections Hematuria and hemospermia

#### **Less Common Signs**

Pain Fever Urethral obstruction Infertility Gait abnormalities

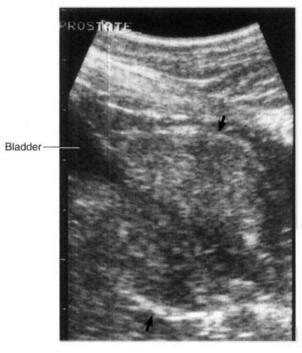


FIG 62-1 Sonogram of normal canine prostate (arrows) of an English Setter. Hatch marks represent 1 cm.

to the level of the prostate, as determined by rectal palpation; the prostate is thoroughly massaged by way of the rectum; and additional material is aspirated through the catheter. The prostatic urethra can be lavaged with sterile saline solution if an inadequate volume is recovered. The premassage and postmassage specimens are analyzed and compared. A urethral brush may also be used to obtain material for cytologic and microbiologic evaluation. In this method the brush is passed through a urinary catheter to the level of the prostate, as determined by rectal palpation. The prostatic urethra is then "brushed."

Prostatic massage is easily performed. There is a risk of rupturing prostatic abscesses or liberating septic emboli during massage. Because prostatic fluid normally refluxes into the urinary bladder, urinary tract infection is usually present whenever there is bacterial prostatitis. Conversely, urinary tract infection can exist in the absence of prostatitis. If a urinary tract infection is present, microbiologic and cytologic examination of the prostatic portion (third fraction) of the ejaculate to confirm the presence of bacterial prostatitis is more accurate than examination of specimens obtained by massage. Neoplastic cells may not be recovered in specimens obtained by prostatic massage or brush unless there is urethral invasion.

Fine-needle aspiration is an excellent method to obtain prostatic specimens for cytology and culture. Fine-needle aspiration is usually performed percutaneously, preferably with ultrasound guidance. A transrectal approach for fine-needle aspiration has also been described. The percutaneous approach is generally safe and simple if a careful technique, especially with ultrasound guidance, is used. Percutaneous ultrasound-guided biopsy of the prostate can also be performed. Prostatic biopsy is also performed via a celiotomy. After prostatic biopsy there may be mild, transient hematuria that resolves spontaneously.

#### BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is the most common prostatic disorder in the dog. Some degree of BPH is found in most intact male dogs older than 6 years of age. It occurs as a result of androgenic stimulation. Specifically, it is mediated by dihydrotestosterone, which causes symmetric prostatic growth. Why some males are affected and others are not is unknown. BPH is often a subclinical incidental finding on routine examination of older dogs. When clinical signs are present, the most common are tenesmus and prostatic bleeding reflected by blood dripping from the urethra in the absence of urination. This bleeding may be exacerbated by sexual arousal. Macroscopic or microscopic hematuria and hemospermia may also be found (see Box 62-1). Contrary to the situation in men, urine retention is a rare manifestation of BPH in dogs.

#### **Diagnosis**

The diagnosis of BPH is suggested when tenesmus, a sanguineous urethral discharge, hematuria, or a combination of these is found in an otherwise healthy, middle-aged or older, intact dog with symmetric prostatomegaly. Less commonly, dogs with BPH may be evaluated because of blood in the semen. The prostate gland is not painful when palpated. Radiologic studies confirm the presence of prostatomegaly (Fig. 62-2, A). Ultrasound studies should show diffuse, relatively symmetric involvement throughout the prostate (Figs. 62-2, B, and 62-3). Small, multiple, diffuse, cystic structures are commonly seen on ultrasound images obtained in dogs with BPH. Initially, prostatic enlargement is due primarily to glandular hyperplasia. This progresses to cystic hyperplasia. Cytologic examination reveals evidence of hemorrhage and

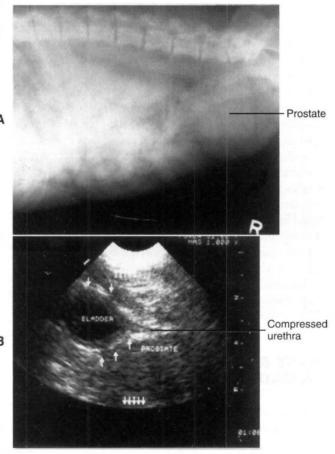


FIG 62-2
Benign prostatic hyperplasia. Radiograph (A) and sonogram (B) from the same dog showing urethral compression. Single arrows, bladder; multiple arrows, prostate.

perhaps mild inflammation but no evidence of sepsis or neoplasia. The diagnosis of BPH could be confirmed by histopathologic studies of biopsy specimens, in which hyperplastic changes, often with microscopic cysts, are found; however, biopsy is rarely necessary.

#### **Treatment**

Treatment is not necessary for asymptomatic BPH, but castration is the treatment of choice for dogs showing clinical signs of BPH. Prostatic involution is usually evident within a few weeks of castration and is complete by 12 weeks after the source of androgens is removed. Prostatic bleeding usually resolves in about 4 weeks. Castration may not be a feasible treatment option for breeding males. Such animals can be treated with antiandrogens, but this is not as effective as castration in resolution of the clinical signs, and the results are temporary. However, it may be many months before signs recur. In addition to castration or antiandrogen therapy, cysts can be treated by fine-needle aspiration under ultrasound guidance. The fluid should be submitted for bacterial culture because many cultures are found to be positive for bacteria (see later discussion of chronic bacterial prostatitis).

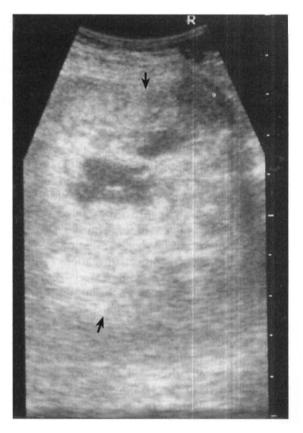


FIG 62-3 Sonogram of the cystic, hyperechoic prostate of a German Shepherd Dog with prostatomegaly  $(5.7 \times 4.6 \text{ cm})$  resulting from benign prostatic hyperplasia. Hatch marks represent 1 cm.

When castration is not a desirable option, antiandrogenic drugs may be considered. Estrogen therapy to reduce prostatic hyperplasia, although initially effective, is not recommended because estrogens can induce squamous metaplasia of the prostate, enhance the cystic changes within the prostate, and depress spermatogenesis. The dose-dependent and idiosyncratic toxic effect of estrogens on canine bone marrow is well known.

Progestins have antiandrogenic effects. At high doses they suppress spermatogenesis and spermatozoal motility, increase morphologic defects in spermatozoa, and suppress serum testosterone concentrations, despite having no apparent effect on serum luteinizing hormone (LH) concentrations. Progestins reportedly also have no apparent effect on libido in dogs, despite the fact that they suppress serum testosterone concentrations. Megestrol acetate at a dosage of 0.5 mg/kg orally, q24h for 10 days to 4 weeks, has been reported to cause the clinical signs of BPH to resolve without adverse effects on fertility in dogs, but its long-term use has not been evaluated. Delmadinone acetate is another progestin that is used to treat BPH. It is administered at a dose of 1.5 mg/kg subcutaneously at weeks 0, 1, and 4. This causes adrenal suppression for up to 21 days after the last dose but no changes in glucose tolerance or growth hormone. It is not as effective as castration in resolving prostatic bleeding. A

single subcutaneous injection of 3 mg/kg of medroxyprogesterone acetate (MPA) relieves the clinical signs of BPH for 10 to 24 months in most dogs treated (84%). Although serum testosterone concentrations were decreased after week 5, there were no apparent problems with semen quality or libido. The effects of progestins on adrenal function, growth hormone secretion, and insulin and glucose homeostasis (see Chapter 56) should be considered.

Finasteride (Proscar®; Propecia®; Merck) inhibits 5-αreductase, thereby inhibiting the conversion of testosterone to dihydrotestosterone. It is not labeled for use in dogs. Doses of 0.1 to 0.2 mg/kg q24h, or 5 mg/dog/day, orally have been studied. Relative to body weight, these doses are much higher than the 5 mg/day recommended for men with BPH. Treatment is continued for several months. Clinical signs begin to improve after 1 week of treatment. Prostatic size is demonstrably and significantly decreased by 8 weeks of treatment because of atrophy of the prostatic epithelium and fibromuscular stroma. Prostatic fluid volume will decrease; otherwise, there is no apparent effect on semen quality. Libido and ejaculation are unaffected. Serum testosterone concentration was unchanged, but serum dihydrotestosterone concentrations were significantly decreased. Although the changes induced by finasteride are reversed by 6 months after the termination of treatment, the prostate gland does not necessarily return to pretreatment sizes. At the 0.1 to 0.2 mg/kg doses, adverse effects were not reported. Finasteride is teratogenic. Therefore pregnant women must not handle the drug.

The concept of immunizing dogs against gonadotropin releasing hormone (GnRH) or LH has appeal for the treatment of BPH. Because GnRH and LH control gonadal function, blocking them would theoretically suppress testosterone production, which in turn would diminish dihydrotestosterone and prostate size. These effects might be maintained permanently or temporarily, depending on the duration of adequate antibody titers. An anti-GnRH factor product (Canine Gonadotropin Releasing Factor Immunotherapeutic®; Pfizer) is marketed in the United States for treatment of benign prostatic hyperplasia in dogs. Treatment also causes the testes to shrink and serum testosterone concentrations to decline, both of which would be deleterious to spermatogenesis.

An over-the-counter medicament made from an extract of the berry from the saw palmetto plant (*Serenoa repens*) has been marketed for relief of some of the urine retention symptoms of BPH in men. There is no evidence that it is beneficial in either dogs or men with BPH (Barsanti, et al., 2000; Bent, et al., 1998). No adverse effects were noted in the treated dogs.

# SQUAMOUS METAPLASIA OF THE PROSTATE

Estrogen-secreting testicular tumors are the most common cause of prostatic squamous metaplasia. Rarely, adrenal tumors and exogenous estrogen therapy also may cause squamous metaplasia of the prostatic epithelium and diminish the movement of prostatic fluid within prostatic ducts. The clinical signs and physical examination findings may be identical to those seen in the setting of BPH. Additional signs of hyperestrogenism (see Box 61-1) may also be present. A testicular mass may be palpable or cryptorchidism may be identified during physical examination. Increased numbers of squamous epithelial cells are often found in ejaculated or aspirated prostatic specimens. If necessary, the diagnosis can be confirmed by prostatic biopsy.

Squamous metaplasia is treated by removing the source of estrogen. This is accomplished by the castration of dogs with testicular tumors or the discontinuation of estrogenic drugs. In the absence of estrogenic drugs, the finding of prostatic squamous metaplasia in a castrated dog strongly suggests the presence of a cryptorchid testicle that was not removed. The effects of estrogen are potentially reversible. Unilateral castration might be considered for a dog that still has potential value as a stud, although it may take some time for the hypothalamic-pituitary-gonadal axis to recover.

# ACUTE BACTERIAL PROSTATITIS AND PROSTATIC ABSCESS

Bacterial infection of the prostate gland may be acute or chronic, and overt prostatic abscesses may develop in dogs with such infections. Normally, the prostate is protected against bacterial colonization by the local production of secretory IgA, the production of prostatic antibacterial factor, and the removal of organisms through frequent micturition. Presumably, the diseased prostate is more prone to infection than the normal gland. Indeed, when cultured, many of the cysts in BPH are found to have asymptomatic infection. The most common route of infection is the ascension of urethral flora. A hematogenous route of infection is also possible. The organisms most commonly isolated from the infected prostate are *Escherichia coli*, *Staphylococcus*, *Streptococcus*, and *Mycoplasma*. Occasionally, *Proteus* spp., *Pseudomonas*, or anaerobic organisms are found.

## Diagnosis

Animals with acute bacterial prostatitis or prostatic abscess usually have a history of an acute onset of severe illness, with abdominal pain and perhaps a hemorrhagic urethral discharge. Fever, dehydration, and pain on palpation of the prostate are usually present. The prostate may be normal in size or enlarged. Asymmetry, prostatomegaly, and fluctuant areas are usually palpable in animals with prostatic abscesses. Septicemia and endotoxemia can develop, in which case signs of shock may also be present. Bacterial prostatitis and prostatic abscess are diagnosed on the basis of the findings from physical examination and ultrasonography and cytology and culture of prostatic fluid. Ultrasonographic examination of the prostate identifies intraparenchymal, fluid-filled spaces consistent with abscesses (Fig. 62-4). A neutrophilic leukocytosis with a variable shift toward immaturity, signs



#### FIG 62-4

Prostatic abscesses in a 5-year-old male Mastiff treated for 1 year with intermittent antibiotic therapy for recurrent *E. coli* urinary tract infection. **A,** Precastration prostate size was  $7.0 \times 3.5$  cm. Largest abscess  $(9.9 \times 9.6$  mm) indicated by marks. **B,** 3 months postcastration prostate size was  $4.8 \times 2.6$  cm. Normal echotexture and all cystic structures resolved. (Notice different magnification of **A** and **B**.)

of toxicity in the neutrophils, and monocytosis are typically shown by a complete blood count in animals with acute infections or abscesses.

Prostatic fluid obtained by ejaculation is a good specimen for bacterial culture and antibiotic sensitivity testing. However, dogs with acute prostatitis or abscess usually are too ill or in too much pain to ejaculate. Prostatic specimens obtained by fine-needle aspiration, preferably with ultrasound guidance, are also acceptable. Cultures of prostatic specimens from dogs with bacterial prostatitis usually yield greater than 10<sup>3</sup> to 10<sup>5</sup> CFUs/ml. Culture of urine is an alternative to culture of prostatic material because normally some prostatic fluid refluxes into the bladder. Urinalysis usually shows hematuria, pyuria, and/or bacteriuria. When urinalysis findings are abnormal, urine should always be submitted for culture and sensitivity testing. Usually, cultures of urine and prostatic material grow the same organisms. Although specimens for culture can also be obtained by prostatic massage, extreme caution should be exercised when massaging the prostate of animals with acute bacterial prostatitis or prostatic abscess because of the risk of rupturing an abscess or the risk of a septic embolism developing. Cytologic evaluation of the prostatic material should be performed. This usually reveals inflammation with evidence of sepsis and hemorrhage, with macrophages found in animals with chronic infection. Unlike the situation in men, prostatic fluid pH, specific gravity, and cholesterol and zinc concentrations typically are not of diagnostic value in dogs.

#### **Treatment**

Acute bacterial prostatitis and prostatic abscesses are serious, life-threatening disorders. Treatment must be prompt and aggressive. Fluid therapy is necessary to correct dehydration and shock. Despite aggressive therapy, the morbidity and mortality associated with prostatic abscesses are high. Large prostatic abscesses are treated most effectively by surgical drainage and omentalization. The abscess may also be drained by fine-needle aspiration under ultrasound guidance. Pending the results of culture and susceptibility, treatment with a fluoroquinolone, ampicillin, or first-generation cephalosporin should be initiated. Antibiotic treatment for acute prostatitis and prostatic abscesses should be continued for a minimum of 4 weeks. Urine or prostatic fluid should be recultured a week after discontinuing antibiotic therapy and again 2 to 4 weeks later to be certain the infection has resolved. Castration should be considered. It can be performed whenever the dog's hemodynamic and metabolic status is stable enough for general anesthesia. Prostatic abscessation has been reported to recur in about 10% of treated dogs.

#### CHRONIC BACTERIAL PROSTATITIS

The primary sign of chronic bacterial prostatitis is recurrent urinary tract infection. Chronic bacterial prostatitis may be asymptomatic. Physical abnormalities are often limited to the urinary tract. Prostatic size and shape may be normal, or the prostate may be asymmetric and more firm than normal. It may or may not be painful to palpation. Ultrasonographic findings are nonspecific but typically will be of mixed echotexture with hyperechoic areas reflecting fibrosis. Confirmation of chronic bacterial prostatitis requires cytologic and microbiologic examination of urine and prostatic material, which may be obtained by fine-needle aspiration.

Chronic bacterial prostatitis may be difficult to eradicate because the blood-prostate barrier is quite effective in preventing many drugs from penetrating into the prostatic parenchyma. Erythromycin, clindamycin, oleandomycin, trimethoprim-sulfonamide, chloramphenicol, carbenicillin, enrofloxacin, and ciprofloxacin are the agents most capable of achieving therapeutic concentrations in the prostate. Antibiotic therapy should be based on culture and susceptibility results from urine and prostatic material. Treatment should be continued for at least 4 weeks. Cultures should be repeated during and for several months after discontinuing antibiotic therapy to ascertain whether resistance to antibiotics or persistent infection has developed. Castration hastens the response to treatment of chronic bacterial prostatitis.

#### PARAPROSTATIC CYSTS

Paraprostatic cysts apparently develop from remnants of the Müllerian duct or as a result of the tremendous enlargement of an existing cyst (prostatic retention cyst). In the former

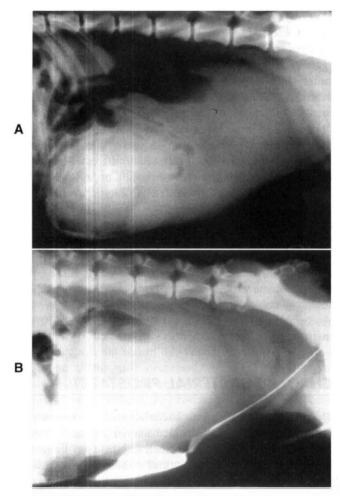


FIG 62-5
Very large, partially calcified paraprostatic cyst. Survey radiograph (A) and cystourethrogram (B) showing bladder displacement.

situation the rest of the prostate gland is essentially normal, whereas in the latter situation cystic benign hyperplasia usually exists. Often, the origin of the cyst is obscure. Paraprostatic cysts are located outside the prostatic parenchyma but are attached to the gland by a stalk or adhesions. These cysts can become extremely large and cause clinical signs, including tenesmus, stemming from mechanical interference with abdominal viscera. Otherwise, they are often asymptomatic.

The possibility of a paraprostatic cyst should be considered in the dog with a large caudal-abdominal mass. Diagnostic imaging will identify the mass as a cystic structure and will help differentiate the cyst from the urinary bladder (Fig. 62-5). Fine-needle aspiration of the paraprostatic cyst usually yields a sterile, yellow-to-serosanguineous fluid showing minimal evidence of inflammation. The treatment is castration and complete surgical excision of the cyst. In situations in which the cyst cannot be completely excised, omentalization is recommended. If this fails to resolve the problem, marsupialization could be performed, but this is a very poor alternative to extirpation or omentalization.

#### PROSTATIC NEOPLASIA

Prostatic adenocarcinoma is the most common neoplasm of the canine prostate. It occurs in older dogs, with a mean age of 10 years at the time of diagnosis. Transitional cell carcinoma arising in the urinary tract may also invade the prostate. The clinical signs and biologic behavior of both tumors in the prostate gland are similar. Prostatic adenocarcinoma is locally invasive and metastasizes to the sublumbar lymph nodes, bony pelvis, and lumbar vertebrae. The link between previous castration and the development of prostatic adenocarcinoma is unclear, but about 50% of affected dogs have been previously castrated. A benign prostatic adenoma has been reported in an intact male dog. Rarely, prostatic adenocarcinoma occurs in cats.

#### **Clinical Features**

Clinical signs include tenesmus and dyschezia, stranguria, pain, gait abnormalities, and weight loss. Palpation of the prostate usually elicits pain. The gland is usually not dramatically enlarged, but the shape may be irregular and the consistency somewhat firmer than normal. Because prostatic involution, resulting in a small gland, occurs within 12 weeks of castration, prostatic neoplasia should be the primary consideration in a previously castrated male dog found to have a "normal"-size or large prostate. Urinary obstruction rarely occurs in dogs as a result of prostatic diseases other than prostatic neoplasia, but it is fairly common in those with cancer.

#### Diagnosis

The diagnosis of prostatic neoplasia is suggested by the history, physical, and the findings of diagnostic imaging. Prostatic adenocarcinoma is usually hyperechoic relative to the normal prostate, but this is not pathognomonic. The finding of urethral invasion demonstrated by contrast radiologic studies or ultrasonography is highly suggestive of neoplasia. The diagnosis is confirmed by fine-needle aspiration or biopsy findings. Neoplastic cells may be found in specimens aspirated through a urethral catheter, especially if the tumor has invaded the urethra. Usually, neoplastic cells are not found in ejaculate specimens. The serum and seminal plasma concentrations of acid phosphatase and prostatespecific antigen are not different between normal dogs and dogs with prostatic disease. Although prostate-specific esterase concentrations are higher in dogs with prostatic disease than in normal dogs, this finding is not specific to the cause of prostatic disease.

# **Treatment**

The prognosis for dogs in which prostatic adenocarcinoma arose after castration is much worse than for dogs that are intact at the time. Prostatic adenocarcinoma in intact dogs is likely to be somewhat hormone responsive, and castration may be a beneficial part of the therapy. Prostatic adenocarcinoma in previously castrated dogs is likely to be refractive to hormonal therapy. To date, surgical (prostatectomy),

chemotherapeutic, and radiation therapy have been largely unsuccessful in improving the quality or length of life. Treatment with the nonsteroidal antiinflammatory drug piroxicam may offer some relief. Consultation with a veterinary oncologist is recommended.

# **Suggested Readings**

Barsanti J: Genitourinary infections. In Greene C, editor: Infectious diseases of the dog and cat, ed 3, St Louis, 2005, WB Saunders.

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Court E et al: Effects of delmadinone acetate on pituitary-adrenal function, glucose tolerance, and growth hormone in male dogs, *Aust Vet J* 76:555, 1998.

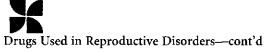
Johnston S et al, editors: Canine and feline theriogenology, Philadelphia, 2001, WB Saunders.

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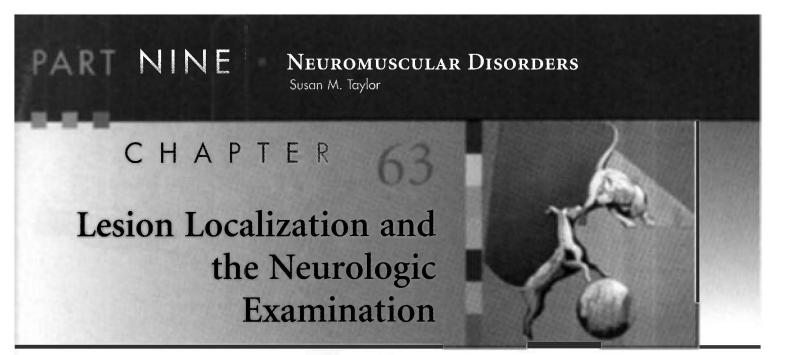
# Drugs Used in Reproductive Disorders

(Note: Many of these drugs are extra-label use in small animals. Many dosages are micrograms, µg. Most have various sources, even if only one is listed herein.)

USE	DRUG	TRADE NAME	CANINE DOSE	FELINE DOSE
Abortifacient	Cloprostenol	Estrumate, Mallinckrodt	begin 25 days after LH, 1 μg/kg, SC, q48h, plus bromocriptine, 30 μg/kg, PO, q8h OR plus cabergoline, 5 μg/kg, PO,	
	A - l i - t	Ali-ina Vialana	q24h	10 15 /k-
	Aglepristone	Alizine, Virbac	10 mg/kg, SC, twice, 24 hours apart	10 or 15 mg/kg, SC, twice, 24 hours apart
	Cabergoline	Galastop, Beringer- Ingeheim; Dostinex, Pfizer	5 μg/kg, PO, q24h, 3-5 days, begin ≥ day 49	'
	$PGF_{2\alpha}$	Lutalyse, Pfizer	0.1-0.25 mg/kg, SC, q8-12h, begin ≥ day 35, until abortion complete <b>OR</b>	0.25-0.5 mg/kg, SC, q12h, begin day 45, until abortion
			0.25 mg/kg, SC, q12h, 4 days, begin during cytologic diestrus days 8-15, monitor progesterone	complete
Agalactia	Oxytocin	Various	0.5-2.0 U/dog, SC, 30 minutes before nursing for milk let- down	
	Metoclopramide	Reglan, Wyeth-Ayerst	0.1-0.2 mg/kg, PO or SC, q6- 8h for milk production	
Benign prostatic hyperplasia	Finasteride	Proscar and Propecia, Merck	0.1-0.5 mg/kg <b>OR</b> 5 mg/dog, PO, q24h	
	Anti-GnRH vaccine	Canine GnRF- immunotherapeutic, Pfizer	SC, at 0 and 4 weeks	
	Medroxyprogesterone	Depo-Provera, Pfizer	3 mg/kg, SC, once	
	Megestrol acetate	Ovaban, Shering	0.5 mg/kg, PO, q24h, 10 or more days	
	Delmadinone	Tarđak, Pfizer	1.5 mg/kg, SC, at 0, 1, and 4 weeks	



USE	DRUG	TRADE NAME	CANINE DOSE	FELINE DOSE
Dystocia*	Calcium gluconate IV	Various	10% solution, slow IV ≤ 0.2 <b>ml</b> /kg	
*No obstruction	Oxytocin	Various	maintain normal labor pattern 0.25-4.0 U/dog, IM maintain	
			normal labor pattern	
Estrus induction during anestrus	Cabergoline	Galastop, Beringer- Ingeheim; Dostinex, Pfizer	5 μg/kg, PO, q24h, until 2-5 days after onset of proestrus	
	Bromocriptine	Lactafal, Eurovet BV; Parlodel, Sandoz	5 or 20 μg/kg, PO, q12h, until onset of proestrus	
	Deslorelin	Ovuplant, Fort Dodge	1.05 or 2.1 mg, SC implant in vestibular mucosa in ventral commissure of vulva	
Estrus suppression	Megestrol acetate	Ovaban, Shering	Within first 3 days of proestrus, 2.2 mg/kg, PO, daily for 8 days, <b>OR</b> during anestrus, 0.55 mg/kg, PO, daily for 32 days	
	Medroxyprogesterone	Depo-Provera, Pfizer; Various	3 mg/kg, SC, once, <b>OR</b> 5 mg/bitch/day, PO, daily for 1-2 weeks	
	Testosterone- propionate	Various	110 mg, IM or SC, q7 days	
	cypionate methyltestosterone		2 mg/kg, IM, q14 days 25-50 mg, PO, twice weekly	
False	Deslorelin Banana printina	Ovuplant, Fort Dodge	6-12 mg, SC implant*	6 mg, SC implant
pregnancy	Bromocriptine	Lactafal, Eurovet BV; Parlodel, Sandoz	* may initially induce estrus 10 μg/kg, PO, q12h, 10-14 days	
, ,	Metergoline Cabergoline	Contralac, Virbac Galastop, Beringer- Ingeheim;	0.1 mg/kg, PO, q12h, 8 days 5 μg/kg, PO, q24h, 4-7 days	
Follicular ovarian cysts	GnRH	Dostinex, Pfizer Cystorelin, Abbott; Various	2.2 μg/kg, IM, q24h, 3 days	
Increase sperm ejaculated	$PGF_{2\alpha}$	Lutalyze, Pfizer	0.1 mg/kg, SC, 15 minutes before collection	
Induce parturition	Aglepristone	Alizine, Virbac	15 mg/kg, SC, twice on one day	
Infertility with short	Megestrol acetate	Ovaban, Shering	2 mg/kg, PO, 8 days, begin within first 3 days of proestrus	
interestrous interval	Chlormadinone	Various	0.5 mg/kg, PO, 8 days, begin within first 3 days of proestrus	
Mammary hyperplasia	Aglepristone* *will cause abortio	Alizine, Virbac in <b>if pregnant</b>	not applicable	20 mg/kg, SC once, <b>OR</b> 10 mg/kg, SC, 2 consecutive days
Ovulation induction	GnRH	Cystorelin, Abbott	50-100 μg/dog, IM, once, <b>OR</b> 2.2 μg/kg, IM, once	25 µg/cat, IM, once or twice, q24h
during estrus	hCG	Various	10-22 IU/kg, IM, once	250 IU/cat, IM, once or twice, q24h
Puerperal hypocalcemia	Calcium gluconate IV, followed by Ca	Various	10% solution, slow IV, to effect [3-20 ml]	10% solution, slow IV, to effect
Pyometra	gluconate, lactate, or carbonate PO See Box 57-2	Example: Tums	1-3 g, PO, q24h	500-600 mg, PO, q24h



# CHAPTER OUTLINE

FUNCTIONAL ANATOMY OF THE NERVOUS SYSTEM AND LESION LOCALIZATION

Brain

Spinal Cord

Neuromuscular System

Neurologic Control of Micturition

SCREENING NEUROLOGIC EXAMINATION

Mental State

Posture

Gait

Postural Reactions

Muscle Size/Tone

Spinal Reflexes

Sensory Evaluation

Pain/Hyperpathia

**Urinary Tract Function** 

Cranial Nerves

Lesion Localization

#### DIAGNOSTIC APPROACH

Animal History

Disease Onset and Progression

Systemic Signs

# FUNCTIONAL ANATOMY OF THE NERVOUS SYSTEM AND LESION LOCALIZATION

The most important step in the diagnostic evaluation of dogs or cats with neurologic signs is establishing an accurate anatomic diagnosis (Box 63-1). A basic understanding of nervous system structure and function is essential to correctly interpret neurologic examination findings and localize lesions to clinically significant regions.

#### **BRAIN**

The brain consists of the cerebrum, the brainstem, and the cerebellum. The brainstem is further subdivided from rostral to caudal into the diencephalon (thalamus and hypothalamus), midbrain, pons, and medulla oblongata (Fig. 63-1). Neurologic abnormalities within the brain can usually be localized on the basis of clinical findings to one of three clinically important regions. These include (1) the forebrain (the cerebrum and diencephalon), (2) the pons and medulla, and (3) the cerebellum (Box 63-2).

#### **Forebrain**

The forebrain includes the cerebral cortex, cerebral white matter, basal nuclei, and the diencephalon. The cerebral cortex is important for behavior; vision; hearing; fine motor activity; and conscious perception of touch, pain, temperature, and body position (proprioception). The cerebral white matter transmits ascending sensory information and descending motor signals, and the basal nuclei are involved in maintaining muscle tone and the initiation and control of voluntary motor activity. Unilateral forebrain lesions result in a relatively normal gait but postural reaction deficits and increased muscle tone in limbs on the contralateral (opposite) side of the body. The diencephalon is important in the integration of sensory input, maintenance of consciousness and attention, and control of autonomic and endocrine functions such as appetite, thirst, temperature, electrolyte, and water balance. The olfactory nerve, cranial nerve 1 (CN1), projects onto the hypothalamus, and the optic nerve (CN2) and optic chiasm are on the ventral surface of the hypothalamus; therefore lesions in this region can result in loss of the sense of smell or contralateral visual deficits with normal pupillary light reflexes. Neurologic examination findings associated with forebrain lesions are listed in Box 63-3.

#### Pons and Medulla

The pons and medulla compose the portion of the brainstem that contains the regulatory centers for consciousness



# BOX 63-1

#### Steps in Neurologic Diagnosis

- 1. Describe the neurologic abnormalities.
- 2. Localize the lesion.
- 3. Describe any concurrent nonneurologic disease.
- Characterize the onset and progression of the neurologic disease.
- 5. Generate a list of differential diagnoses.
- Use ancillary tests, if needed, to make a diagnosis and gauge the prognosis.



# BOX 63-2

#### Clinically Important Neuroanatomic Regions

#### **Brain**

Forebrain

Cerebrum

Diencephalon (thalamus and hypothalamus)

**Brainstem** 

Midbrain

Pons

Medulla oblongata

Cerebellum

#### **Spinal Cord**

C1-C5

C6-T2 (cervical intumescence)

T3-L3

L4-S3 (lumbar intumescence

#### **Neuromuscular System**

Peripheral nerves

Neuromuscular junction

Muscle

(ascending reticular activating system) and normal respiration. This area provides a link between the spinal cord and the cerebral cortex through ascending sensory and descending motor tracts. These tracts cross in the rostral midbrain, such that while unilateral forebrain lesions result in contralateral limb deficits, unilateral lesions of the pons, medulla, or spinal cord cause ipsilateral (same side) deficits. Ten pairs of cranial nerves (3 to 12) originate in this region, with lesions reflecting motor or sensory dysfunction of individual nerves. Because vestibular nuclei are located in the medulla oblongata and the flocculonodular lobe of the cerebellum, lesions at this site commonly result in head tilt, disequilibrium, and nystagmus (see Chapter 68). Box 63-3 lists common neurologic examination abnormalities in patients with lesions of the pons and medulla.

## Cerebellum

The cerebellum controls the rate, range, and force of movements. It serves to coordinate muscular activity, regulate fine

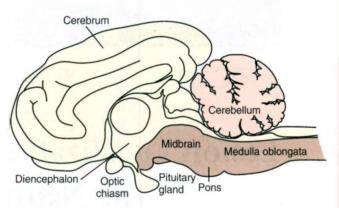


FIG 63-1 Regional anatomy of the brain.



## BOX 63-3

#### Signs Caused by Lesions in the Brain

#### Forebrain Lesions

Seizures

Altered mentation: depression, stupor, coma

Abnormal behavior: agitation, delirium, aggression, loss of

learned behaviors

Contralateral:

Blindness with normal pupillary light reflexes Subtle decrease in skin/facial sensation

Hemi-inattention syndrome

Normal gait

Circling, pacing towards lesion

+/- Postural reaction deficits in contralateral limbs

Normal or increased (contralateral) spinal reflexes

#### **Brainstem Lesions**

Altered mentation: depression, stupor, coma

Multiple cranial nerve deficits (CN3-CN12, ipsilateral)

Upper motor neuron tetraparesis or hemiparesis

(ipsilateral)

Postural reaction deficits ipsilateral limbs

Normal or increased (ipsilateral) spinal reflexes

Respiratory and cardiac abnormalities

#### Cerebellar Lesions

Normal mentation

Ipsilateral menace deficit +/-

Intention tremor

Hypermetric gait, truncal ataxia with normal strength

Normal knuckling and hopping (hypermetric ipsilateral)

Normal spinal reflexes

Possible paradoxical vestibular syndrome

movement, and modulate muscle tone. Lesions of the cerebellum result in a wide-based stance, ataxia (incoordination) with normal strength, and increased muscle tone (spasticity). The gait is hypermetric or exaggerated, with each limb being raised excessively during protraction and then returned more forcefully than normal to weight bearing. Cerebellar

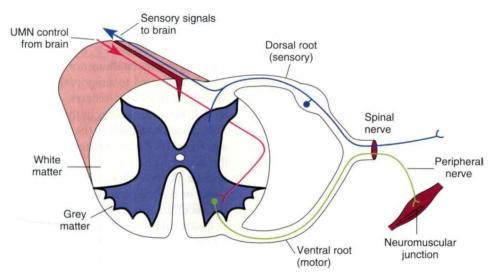


FIG 63-2 A single spinal cord segment.

lesions may also result in a fine tremor of the head that becomes more pronounced during voluntary movement such as reaching for food (intention tremor). Severe lesions of the rostral cerebellum result in opisthotonus with rigid extension of the forelimbs (decerebellate posture) (see the discussion of posture, p. 989). Box 63-3 lists the clinical signs caused by lesions of the cerebellum. Cerebellar disorders are discussed in Chapter 65.

# SPINAL CORD

The spinal cord resides entirely within the bony vertebral column. It is composed of a central H-shaped core of gray matter surrounded by white matter. Spinal cord gray matter contains the cell bodies of interneurons and lower motor neurons (LMNs). White matter is composed of nerve fibers organized into columns of ascending and descending tracts. These long tracts transmit ascending sensory information (proprioception, touch, temperature, pressure, and pain) and descending motor signals between higher centers in the brain and spinal cord neurons.

The spinal cord can be functionally divided into segments, with each spinal cord segment giving rise to one pair of spinal nerves (left and right), each of which has a dorsal (sensory) and ventral (motor) root (Fig. 63-2). The cell bodies for the LMNs supplying the thoracic limbs are in the ventral gray matter within a thickened region of the cord called the cervical intumescence (segments C6-T2), whereas the LMNs supplying the pelvic limbs originate in the lumbar intumescence (segments L4-S3; Fig. 63-3). After a neurologic examination, each limb should be characterized as normal or as having upper motor neuron (UMN) or LMN signs. This will allow localization of spinal cord lesions to one of four functional anatomical regions: spinal cord segments C1-C5, C6-T2, T3-L3, or L4-S3 (Box 63-4). Because the ascending and descending tracts to the rear limbs are located peripherally in the cord, it is common for dogs and cats with

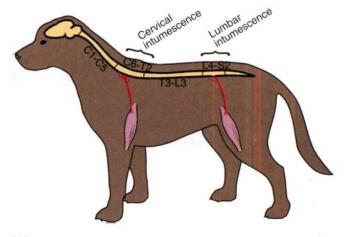


FIG 63-3
Spinal cord segments at the cervical intumescence (C6-T2) and the lumbar intumescence (L4-S3) give rise to the important peripheral nerves of the limbs.

compressive lesions of the cervical (C1-C5) cord to have more pronounced UMN deficits in the rear limbs than in the forelimbs. Also, lesions that affect only the center of the cord (central cord syndrome) in the cranial cervical (C1-C5) or caudal cervical (C6-T2) region will often produce profound UMN (C1-C5) or LMN (C6-T2) deficits in the forelimbs with minimal UMN deficits in the rear limbs.

## **Lower Motor Neuron signs**

The LMN is the efferent neuron that directly connects the central nervous system (CNS) to a muscle or gland (Fig. 63-4). Components of spinal LMNs include the nerve cell bodies within the ventral gray matter, the axons leaving the spinal canal as ventral nerve roots and spinal nerves, and the peripheral nerves formed by the spinal nerves that terminate at the neuromuscular junction in the muscle to produce

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contraction (see Fig 63-2). Damage to any component of the LMN will result in the appearance of LMN signs in the muscles normally innervated by that particular LMN. LMN signs include flaccid paresis (weakness) or paralysis (loss of motor function), decreased or absent muscle tone, rapid muscle atrophy, and decreased or absent spinal reflexes (Table 63-1). When there is damage to the sensory component of the LMN (the peripheral nerve, spinal nerve, or dorsal nerve root), there may also be a loss of sensation in the skin and limb directly supplied by that LMN. Spinal cord lesions causing focal LMN signs are discussed in Chapter 70. Disorders affecting peripheral nerves and disorders causing diffuse LMN paralysis are discussed in Chapter 71.



### BOX 63-4

### Localization of Spinal Cord Disease

### C1-C5

UMN signs forelimbs UMN rear limbs UMN bladder +/-

### C6-T2 (Cervical Intumescence)

LMN signs forelimbs +/- Horners syndrome UMN rear limbs UMN bladder +/-

### T3-L3

Normal forelimbs
UMN rear limbs
UMN bladder +/-

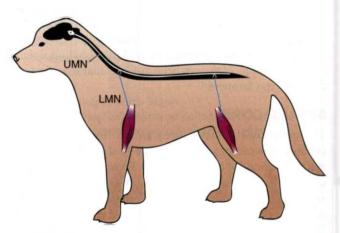
### L4-53 (Lumbar Intumescence)

Normal forelimbs
LMN rear limbs
Loss of perineal sensation and reflex
Dilated anus, fecal incontinence
LMN bladder +/-

UMN, Upper motor neuron; LMN, lower motor neuron.

### **Upper Motor Neuron Signs**

Those motor systems originating in the brain to control the LMN are UMNs (see Fig. 63-4). UMNs are responsible for initiating and maintaining normal movement, regulating the muscle tone used to support the body against gravity, and inhibiting myotactic reflexes. Components of the UMN include nerve cell bodies in the cerebral cortex, basal nuclei, and brainstem as well as the motor tracts in the brainstem and spinal cord white matter, which relay information from the higher centers to the LMN. These pathways cross the midline in the rostral brainstem so that forebrain lesions result in contralateral deficits in the limbs, whereas UMN lesions of the spinal cord, pons, or medulla oblongata result in ipsilateral deficits in the limbs (Fig. 63-5). Damage to the UMN nuclei or tracts will cause loss of voluntary motor function and a release of the inhibitory effect of UMNs on all LMNs caudal to the level of injury. The resultant UMN signs in all muscles caudal to the site of the lesion include spastic paresis or paralysis, increased extensor muscle tone, and normal to increased spinal reflexes (see Table 63-1). Associated sensory signs such as ataxia and decreased sensation in the skin and limbs caudal to the lesion reflect inter-



### FIG 63.4

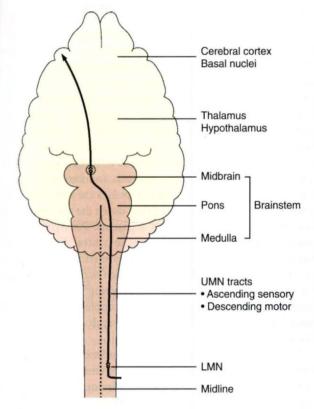
The upper motor neuron (UMN) and lower motor neuron (LMN) systems are responsible for mediating normal motor function.



**TABLE 63-1** 

### Summary of Upper Motor Neuron and Lower Motor Neuron Signs

CHARACTERISTIC	UPPER MOTOR NEURON	LOWER MOTOR NEURON
Motor function	Spastic paresis to paralysis in all limbs caudal to lesion	Flaccid paresis or paralysis at site of lesion
Postural reactions (knuckling)	Often delayed	Normal unless severe lesion
Gait	Wide-based stance, ataxic, long strides, delayed limb protraction	Short strides, limbs maintained under center of gravity
Muscle tone	Normal or increased	Decreased
Muscle atrophy	Late and mild—disuse	Rapid and severe—neurogenic
Spinal reflexes	Normal or increased	Decreased or absent



**FIG 63-5**Ascending (sensory) and descending (motor) upper motor neuron pathways cross midline in the rostral brainstem.

ruption of the UMN sensory tracts responsible for mediating proprioception (position sense) and pain perception.

### **Spinal Cord Sensory Pathways**

Sensory nerves that detect touch, temperature, and pain are distributed to the surface of the body and limbs. There are also sensory nerves responsible for proprioception that originate in the skin, muscles, tendons, and joints. The nerve cell bodies of most of these sensory nerves are located in the ganglia of dorsal nerve roots entering the spinal cord (see Fig. 63-2). Sensory tracts responsible for mediating sensation and conscious and unconscious proprioception ascend the spinal cord and brainstem to the brain. Most of these tracts ascend the ipsilateral spinal cord and cross over in the rostral brainstem to reach the contralateral cerebrum (see Fig 63-5). Patients with a unilateral forebrain lesion will typically experience hypalgesia (decreased sensation) in the limbs, trunk, and face on the opposite side. Damage to the sensory tracts in the spinal cord will disrupt the transmission of sensory and proprioceptive information to the brain (UMN), resulting in signs of ataxia, or incoordination, and the loss of conscious proprioception in all limbs caudal to the site of the lesion. With unilateral spinal cord lesions the deficits will be ipsilateral. If UMN spinal cord lesions are severe, there may also be some loss of superficial skin sensation caudal to the lesion. In addition to the sensory tracts responsible for relaying information to UMN centers regarding superficial sensation and proprioception, there are multisynaptic, small-diameter, bilateral crossing tracts deep in the white matter of the spinal cord that project to the cerebral cortex and are involved in the conscious perception of noxious stimuli (nociception, deep pain). The small diameter and deep location of these tracts make them very resistant to compressive injury, so loss of the ability to perceive a noxious stimulus (loss of deep pain perception) in the rear limbs of an animal with a T3-L3 lesion usually indicates a very severe transverse spinal cord injury.

Loss of sensation caused by damage to spinal cord dorsal gray matter, dorsal nerve roots, or the sensory portion of a peripheral nerve allows the LMN lesion to be precisely localized on the basis of skin sensation mapping. When there is a compressive or irritative lesion of the nerve root or peripheral nerve, there will sometimes be hyperesthesia (pain) at the site.

# **NEUROMUSCULAR SYSTEM Peripheral Nerves**

The peripheral nervous system consists of 12 pairs of cranial nerves originating in the brainstem and 36 pairs of spinal nerves originating in the spinal cord. Nerve fibers from the spinal nerves in the cervical and lumbar intumescences join together to form the peripheral nerves that innervate the muscles of the limbs. Spinal nerve or peripheral nerve lesions result in LMN motor signs in affected muscles and limbs and sometimes decreased, absent, or altered sensation. Box 63-5 lists the clinical signs caused by peripheral nerve lesions. Peripheral nerve disorders are discussed in Chapter 71.

### **Neuromuscular Junction**

At the neuromuscular junction (NMJ) electrical activity is transmitted from nerve axons to muscle fibers, resulting in muscular contraction. This process is mediated through the calcium-dependent release of the neurotransmitter acetylcholine (ACh) from the nerve terminal into the synaptic cleft. ACh diffuses across the synaptic cleft and binds to ACh receptors on the postsynaptic (muscle) membrane, inducing a conformational change and ion flux that result in muscular contraction. ACh is then rapidly removed from the synapse by acetylcholinesterase, readying the synapse for the next nerve impulse. Disorders that interfere with ACh release or inactivation and disorders that alter postsynaptic cholinergic receptor function will adversely affect neuromuscular transmission. Presynaptic neuromuscular junction disorders causing decreased release of ACh result in flaccid tetraparesis and decreased spinal reflexes (see Box 63-5) similar to diffuse peripheral nerve disorders. Myasthenia gravis is a postsynaptic disorder with reduction in the number of functional ACh receptors. The result is partial failure of NMJ transmission and exercise-induced weakness that may improve with rest but normal muscle tone and spinal reflexes. Disorders that interfere with acetylcholinesterase, the enzyme that normally inactivates ACh in the synapse, cause autonomic nervous system overstimulation and neuromuscular



BOX 63-5

Signs Caused by Lesions in the Neuromuscular System

# Peripheral Nerve Lesion: Signs Seen in Affected Limb/Muscle

Flaccid paresis/paralysis
Decreased to absent muscle tone
Rapid and severe muscle atrophy

Decreased or absent spinal reflexes

EMG suggests denervation

Skin sensation decreased or absent if sensory portion of nerve is affected

# Neuromuscular Junction Disorders: Signs Seen in All Limbs

Flaccid paresis/paralysis

Decreased to absent muscle tone

Decreased or absent spinal reflexes

EMG: decreased amplitude of muscle action potential
Normal postural reactions if able to move and weight is
supported

Normal sensation

Myasthenia gravis (post synaptic defect)

- · Paresis, often exacerbated by exercise
- Normal postural reactions
- Normal muscle tone and size
- Normal spinal reflexes

### **Muscle Disorders**

Paresis, may be exacerbated by exercise
Muscle atrophy, pain, or swelling +/Normal postural reactions if weight is supported
Normal spinal reflexes
Normal skin sensation

EMG, Electromyography.

weakness. Myasthenia gravis and other disorders of neuromuscular transmission are discussed in Chapter 71.

### Muscle

Skeletal muscle functions to maintain body posture and produce movement. Generalized weakness (tetraparesis), a stiff and stilted gait, and exercise intolerance are common clinical features in patients with muscle disease (see Box 63-5). Postural reactions and reflexes are normal. Some disorders cause muscle pain and muscle swelling, whereas others cause muscle atrophy and/or fibrosis. Muscle disorders are discussed in Chapter 72.

# NEUROLOGIC CONTROL OF MICTURITION

The physiologic control of micturition is complex and integrated centrally. The pelvic nerves originate in sacral segments S1-S3 and supply parasympathetic innervation to the bladder. Stimulation causes detrussor muscle contraction, bladder contraction, and bladder emptying. The striated skeletal muscle of the external urethral sphincter is under conscious and reflex control and is innervated by the puden-

dal nerve arising from sacral segments S1-S3. Sympathetic innervation to the bladder is supplied through the hypogastric nerves arising in the lumbar segments (L1-L4 in dogs, L2-L5 in cats). Sympathetic stimulation causes detrusor muscle relaxation (β-adrenergic) and contraction of the internal urethral sphincter (α-adrenergic). Sympathetic tone dominates during urine storage, allowing the bladder to distend with urine. As the bladder enlarges, sensory information from bladder wall stretch receptors is transmitted via the sensory portion of the pelvic nerve through ascending spinal cord pathways to the thalamus and cerebral cortex. When it is appropriate to void, impulses are sent from the cerebral cortex to the pons and then down the reticulospinal tract to the sacral spinal cord segments. Parasympathetic stimulation results in detrusor muscle contraction. There is normally simultaneous inhibition of sympathetic tone in the internal urethral sphincter and somatic (pudendal) input to the external urethral sphincter, allowing urine to flow. Damage to any component of this complex system or the connection with UMN centers will result in disorders of micturition.

Sacral spinal cord, nerve root, or pudendal nerve lesions typically result in urinary incontinence and a large bladder that is easily expressed and leaks continuously (LMN bladder). Perineal and bulbocavernosus reflexes are decreased or absent. Mild or moderate UMN lesions (spinal cord above the sacral segments) cause increased urethral tone, making it difficult for patients to void completely. With relatively mild lesions a syndrome of detrussor-urethral dyssynergia may result, wherein involuntary contraction of the urethral sphincter occurs during detrussor contraction, halting urine flow during voiding. Severe UMN spinal cord lesions causing severe paresis or paralysis typically result in a bladder that is enlarged and very difficult or impossible to express manually (UMN bladder). Occasionally, a reflex or automatic bladder will develop 5 to 10 days after acute UMN spinal cord injury, resulting in reflex detrussor contraction and spontaneous partial emptying of the bladder without cortical perception or voluntary control.

# SCREENING NEUROLOGIC EXAMINATION

A screening neurologic examination takes only a few minutes (Box 63-6). Abnormalities of mentation, posture, and gait are initially evaluated. Postural reactions are then evaluated. If abnormalities are detected, evaluation of muscle tone, spinal reflexes, urinary tract function, and sensory perception aids in lesion localization. Finally, cranial nerves are evaluated, and if necessary, localization of a lesion within the brain is attempted.

### MENTAL STATE

Owners should always be asked if they have noticed any changes in their pet's behavior because subtle changes are often not apparent to the examiner. A decreased level of



### BOX 63-6

### Components of the Neurologic Examination

Mental state Posture Gait Paresis/paralysis Ataxia Proprioceptive (UMN) Vestibular Cerebellar Circling Lameness Postural Reactions Knuckling Hopping Wheelbarrowing Hemiwalking Muscle tone and size Spinal reflexes Perineal reflex/anal tone Sensory perception (nociception) Cranial nerves



### TABLE 63-2

### Disorders of Consciousness

STATE	CHARACTERISTIC
Normal	Alert; responds appropriately to
	environmental stimuli
Depressed	Quiet or drowsy, responds to environmental
	stimuli; obtunded
Delirious	Alert; responds inappropriately to stimuli;
	agitated or confused
Stuporous	Unconscious, except when aroused by
	strong (often painful) stimuli
Comatose	A state of deep unconsciousness from
	which the animal cannot be aroused,
	even with noxious stimuli
	CTCH THIN HOMOUS SIMION

consciousness, such as depression, stupor, or coma (Table 63-2), may occur with a metabolic disturbance or damage or disease affecting the cerebrum or brainstem. Delirium, confusion, or agitation suggests either cerebral cortical disease or a metabolic encephalopathy. Seizures occur with forebrain lesions or functional disturbances secondary to metabolic encephalopathies or intoxications. Aggression, compulsive pacing, loss of housebreaking, vocalizing, and head pressing can all be seen with a forebrain lesion. A behavioral syndrome in which animals with a structural unilateral forebrain lesion ignore all sensory input from the contralateral half of their environment has been called hemi-inattention syndrome.



FIG 63-6
Wide-based stance and excessive limb abduction indicative of ataxia in a 2-year-old Boxer with Neospora caninum meningoencephalomyelitis affecting the cervical spinal cord and cerebellum.

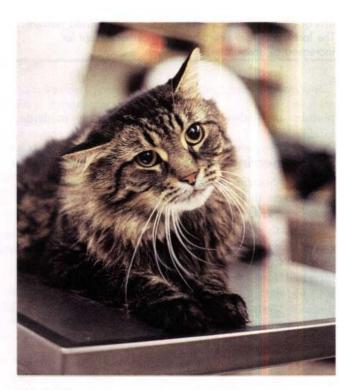


FIG 63-7
Right-sided head tilt in an adult cat with right-sided peripheral vestibular disease caused by otitis media/interna.

### **POSTURE**

A normal upright posture is maintained through the integration of multiple CNS pathways and spinal reflexes. Abnormal postures reflect a disruption of this normal integration. A wide-based stance is common in ataxic animals, particularly those with cerebellar or vestibular disease (Fig. 63-6). A continuous head tilt with resistance to straightening is usually associated with an abnormality of the vestibular system (Fig. 63-7). In recumbent animals



FIG 63-8

Schiff-Sherrington posture in a 9-year-old Lhaso Apso caused by traumatic fracture and luxation of the spine at T11-T12, with damage to the spinal cord at that site. There was a loss of proprioception, loss of voluntary motion, and loss of deep pain in the rear limbs, with increased reflexes. The forelimbs were neurologically normal except for increased extensor tone.

posture and other neurologic findings aid in lesion localization.

### **Schiff-Sherrington Posture**

The Schiff-Sherrington posture is observed in dogs when an acute, severe thoracic or cranial lumbar spinal cord lesion (usually a fracture/luxation, infarction, or hemorrhage) interferes with the normal ascending inhibition of thoracic limb extensor motor neurons by border cells in the spinal cord from L1 to L7 (most from L2 to L4). Forelimbs exhibit increased extensor tone with normal voluntary motion, strength, and conscious proprioception (Fig. 63-8). The rear limbs are paralyzed with normal to increased reflexes (UMN). This posture suggests severe spinal cord damage but does not have prognostic significance.

### **Decerebrate Rigidity**

This posture is most commonly observed when there is a rostral brainstem (midbrain) lesion. Affected animals are stuporous or comatose, all limbs are rigidly extended, and there is dorsal extension of the head and neck (opisthotonus; Fig. 63-9A).

### **Decerebellate Rigidity**

The rostral portion of the cerebellum is responsible for inhibition of excessive extensor muscle tone. A lesion in this region will result in increased thoracic limb extensor muscle tone, opisthotonus, and normal mentation. Rear limbs typically have the hips flexed forward as a result of increased iliopsoas muscle tone. This posturing can be episodic (see Fig. 63-9B and C).

### GAIT

Clinical evaluation of gait involves observation of the animal's movements during walking on a flat, nonslippery surface, with frequent turns and circling. If the animal is unable to walk unassisted, it should be supported with a harness or sling so that voluntary movement and gait can be better assessed. Each patient must be evaluated for paresis (weakness), ataxia, lameness, and circling.

### **Paresis**

Paresis is defined as weakness or inability to support weight or generate a normal gait. Paralysis is the term used to describe paresis so severe that all voluntary movement is lost (Table 63-3). Paresis occurs with LMN or UMN lesions, but the gait that results is markedly different between the two. Animals with LMN disease are usually profoundly weak, and they take small steps, always maintaining their feet under their center of gravity. Their short-strided gait is commonly mistaken for an orthopedic lameness, and they may tremble or collapse with minor exertion. Attempts to move quickly may result in a bunny-hopping gait. In contrast, animals with UMN lesions have a delay in the onset of protraction (the swing phase) and a longer than normal stride with a variable degree of spasticity or stiffness of the limbs. Animals with UMN lesions are ataxic as a result of disruption of the general proprioceptive (sensory) tracts that accompany the UMN tracts.

### **Ataxia**

Ataxia, or incoordination, is caused by lesions of the cerebellum, vestibular system, or the general proprioceptive (GP) sensory tracts in the spinal cord and caudal brainstem (Box 63-7). Animals with GP ataxia lose awareness of where their limbs are in space. They have a wide-based stance, long strides, excessive abduction of limbs during turning, exaggerated limb movements, and a tendency to scuff or knuckle affected limbs while walking. When affected animals are walking, their limbs may cross and the weight-bearing phase may be prolonged because of delayed protraction of affected limbs. Vestibular ataxia is manifested primarily as a loss of balance, reflected in a head tilt and a wide-based, crouched stance with a tendency to lean, drift, fall, or roll to the side. Vestibular ataxia is often accompanied by an abnormal nystagmus (see Chapter 68). Cerebellar ataxia reflects an inability to control the rate, range, and force of movement. Affected animals will have a wide-based stance, swaying of the body from side to side (truncal ataxia), and exaggerated (hypermetric) limb movements with normal strength and increased muscle tone (Fig. 63-10). A fine head tremor may be present (see Chapter 65).

### Lameness

Animals are lame when normal movement causes discomfort. If all limbs are equally painful, they may develop a stiff, short-strided gait, as seen in animals with polyarthritis. Animals with lameness affecting one limb have a short weight-bearing phase in the affected limb and a longer than





FIG 63-9

Abnormal postures. **A,** Decerebrate rigidity. **B,** Decerebellate rigidity. **C,** Decerebellate rigidity in a 6-month-old Labrador Retriever with intracranial hemorrhage following warfarin intoxication.



### **TABLE 63-3**

### Localizing Lesions Causing Paresis and Paralysis

### Tetraparesis/Tetraplegia: Paresis or Paralysis of All Four Limbs

Normal conscious proprioception and spinal

reflexes

LMN fore and rear

LMN forelimbs, UMN rear limbs UMN forelimbs, UMN rear limbs

Nonneurologic disorders (cardiac disease, hypoglycemia, electrolyte abnormalities, hypoxemia)

Myasthenia gravis

Generalized muscle disorders

Generalized disorders of spinal cord ventral gray matter, ventral nerve roots, peripheral nerves or neuromuscular junction

C6-T2 spinal cord C1-C5 or brainstem

### Paraparesis/Paraplegia: Paresis or Paralysis of Rear Limbs

Normal forelimbs, LMN rear limbs

L4-S3 spinal cord
Normal forelimbs, UMN rear limbs

T3-L3 spinal cord

### Monoparesis/Monoplegia: Paresis or Paralysis of One Limb

LMN Lesion of the LMN directly innervating the affected limb (motor neuron

cell body in ventral spinal cord gray matter, ventral nerve roots,

spinal nerves, peripheral nerves)

Ipsilateral T3-L3 spinal cord

### Hemiparesis/Hemiplegia: Paresis or Paralysis of Both Limbs on One Side

LMN fore, UMN rear UMN fore, UMN rear

Rear limb UMN

C6-T2 ipsilateral spinal cord

C1-C5 ipsilateral spinal cord; ipsilateral brainstem; contralateral forebrain lesion

LMN, Lower motor neuron; UMN, upper motor neuron.

normal weight-bearing phase in the contralateral limb. In some cases the painful limb will be elevated or carried. Lameness affecting one limb is common in animals with orthopedic disease but can also be a prominent feature in animals with entrapment (pinching) of a spinal nerve or nerve root by a lateralized disk extrusion or nerve root tumor.

### Circling

Circling can be caused by lesions of the forebrain or the vestibular system. Dogs with unilateral forebrain lesions will usually walk or pace in wide circles toward the side of the lesion. Tight circling toward the side of the lesion is more often associated with vestibular disorders (Fig. 63-11). Most animals with vestibular disease also exhibit head tilt and nystagmus.



FIG 63-10

Exaggerated (hypermetric) limb movements in a Miniature Poodle with granulomatous meningoencephalitis affecting the cerebellum.



BOX 63-7

Localizing Ataxia

### Spinal Cord (Proprioceptive) Ataxia

Paresis of affected limbs
Imability to recognize limb position
Wide-based stance
Long strides
Excessive abduction of limbs during turning
Abnormal postural reactions
Normal mentation and cranial nerves

### Vestibular Ataxia

Head tilt
Wide-based, crouched posture
Balance problem
Peripheral: normal postural reactions
Central: abnormal postural reactions

### Cerebellar Ataxia

Normal strength
Wide-based stance
Hypermetric limb movements
Truncal sway
Normal postural reactions
Intention tremor of the head

### **POSTURAL REACTIONS**

The complex series of responses that maintain an animal in an upright position are called *postural reactions*. Postural reaction testing is used to determine whether animals can recognize the position of their limbs in space (conscious proprioception). Sensory receptors for proprioception originate in the muscles, tendons, and joints, and spinal cord



FIG 63-11
Tight circling and head tilt to the right in a 3-year-old Maltese with inflammatory disease affecting the right forebrain and brainstem.

proprioceptive tracts relay this sensory information to the cerebral cortex. Most proprioceptive tracts ascend the ipsilateral spinal cord and cross midline in the rostral brainstem (see Fig. 63-5). Abnormalities detected during the manipulations performed to test postural reactions do not provide precise localizing information but are sensitive indicators that suggest the presence of neurologic dysfunction somewhere along the neurologic pathway. A careful and systematic evaluation of postural reactions may permit the examiner to detect subtle deficits not observed during routine gait examination and to determine whether each limb is neurologically normal or abnormal. Postural reaction testing should include knuckling, hopping, wheelbarrowing, and hemiwalking (Fig. 63-12). When performed by an experienced clinician comparing the right and left limbs in an animal that has voluntary movement, hopping is the most sensitive and reliable postural reaction test. In animals with significant weakness it is important to support most of the body weight during postural reaction testing. Animals with neuromuscular disorders that still have normal sensation and the ability to voluntarily move their limbs will hop quickly (normal) as long as their weight is supported because their proprioception is normal. For the purpose of lesion localization, abnormalities of postural reaction testing are usually interpreted as UMN signs, which must then be confirmed with testing of muscle tone and spinal reflexes (see Box 63-4 and Table 63-1).



### FIG 63-12

Postural reaction testing. A, Conscious proprioception (knuckling) is evaluated by placing the dorsal surface of the animal's paw on the floor while the animal's weight is supported. The normal response is an immediate return to a normal position. B, Forelimb hopping. The animal is supported under the abdomen, and one thoracic limb is lifted from the ground. The animal is leaned and moved laterally toward the limb being evaluated. The normal animal responds by quickly lifting and replacing the limb under its body as it moves laterally. C, Pelvic limb hopping. The animal is supported under the chest, and one pelvic limb is lifted. The animal is leaned and moved laterally toward the limb being evaluated. The normal animal responds by quickly lifting and replacing its limb under the body as it moves laterally. D, Wheelbarrowing. The animal is supported under the abdomen and moved forward. The head may be elevated to remove visual input and accentuate proprioceptive abnormalities, as shown here. E, Hemiwalking. The front and rear limbs on one side are lifted, and forward and lateral walking movements are evaluated.



### MUSCLE SIZE/TONE

Muscle atrophy and muscle tone should be assessed by careful palpation and movement of each limb through a range of motion. Muscle atrophy can occur slowly as a result of disuse or rapidly as a result of a lesion of the LMN supplying a muscle (neurogenic atrophy). If focal muscle atrophy is detected in a limb, this can be used to precisely localize lesions of the peripheral nerve, nerve roots, or spinal cord gray matter because the spinal cord segments and peripheral nerves responsible for innervating each of the individual limb muscles are well known. Muscle swelling or enlargement is a feature of some myopathies. Muscle tone is generally decreased in animals with significant lesions of the LMN, whereas extensor muscle tone is usually increased with UMN lesions (see Table 63-1). Extreme alterations in muscle tone can be seen in animals with Schiff Sherrington syndrome and with decerebrate and decerebellar rigidity (see Figs. 63-8 and 63-9).

### SPINAL REFLEXES

Spinal reflex evaluation is the most reliable way to classify a neurological disorder as being UMN or LMN. Spinal reflexes and muscle tone will be diminished to absent in LMN disorders and normal to increased in UMN disease. Spinal limb reflexes are best assessed in a relaxed animal restrained in lateral recumbency. Each reflex is judged to be absent (0), decreased (+1), normal (+2), or increased (+3 or +4). Significant LMN lesions will reliably cause an absent or decreased reflex. UMN lesions cause an increased reflex that will not always be distinguishable from normal. In the absence of other neurologic deficits an exaggerated reflex means little and can be observed in an excited or nervous

animal. The limb reflexes that are most useful in dogs and cats include the patellar reflex, the sciatic reflex, the pelvic limb withdrawal (flexor) reflex, and the thoracic limb withdrawal (flexor) reflex. Because other reflexes are found inconsistently in normal animals, they are not routinely evaluated. The spinal reflexes and the spinal cord segments responsible for mediating each reflex are listed in Table 63-4.

### **Patellar Reflex**

With the animal restrained in lateral recumbency, the examiner evaluates the upper (nonrecumbent) limb by holding the stifle in partial flexion and striking the patellar ligament with the flat surface of the reflex hammer (pleximeter), stretching the fibers of the quadriceps muscle (Fig. 63-13). The normal response is a reflex contraction of the quadriceps muscle. This is a monosynaptic myotactic (stretch) reflex, with both sensory and motor components contained in the femoral nerve and the L4, L5, and L6 spinal nerves; nerve roots; and spinal cord segments. A weak or absent patellar reflex indicates a lesion of the femoral nerve or the L4-6 spinal cord segments or nerve roots. A lesion cranial to the L4 spinal cord segment will typically cause an exaggerated reflex. Although this is the most reliable tendon reflex for evaluation, it is sometimes difficult to interpret the response. Occasionally, a lesion of the sciatic nerve or the L6-S2 spinal cord segments will cause the patellar reflex to appear increased by decreasing tone in the muscles opposing stifle extension (pseudohyperreflexia). The patellar reflex can be difficult to elicit in animals with significant orthopedic disease of the stifle, and rarely it is decreased or absent in normal dogs (especially large-breed puppies).



TABLE 63-4

**Spinal Reflexes** 

REFLEX	STIMULUS	NORMAL RESPONSE	SPINAL CORD SEGMENTS
Thoracic limb withdrawal	Pinch foot of forelimb	Withdraw limb	C6, C7, C8, T1, (T2)
Patellar	Strike patellar ligament	Extension of stifle	L4, L5, L6
Pelvic limb withdrawal	Pinch foot of rear limb	Withdraw limb	L6, L7, S1, (S2)
Sciatic	Strike sciatic nerve between greater trochanter and ischium	Flexion of stifle and hock	L6, L7, S1, (S2)
Cranial tibial	Strike belly of cranial tibial muscle just below proximal end of tibia	Flexion of hock	L6, L7 (\$1)
Perineal	Stimulate perineum with pinch	Anal sphincter contraction, ventroflex tail	S1, S2, S3, pudendal nerve
Bulbourethral	Compress vulva or bulb of penis	Anal sphincter contraction	S1, S2, S3, pudendal nerve
Cutaneous trunci	Stimulate skin over dorsum just lateral to vertebral column	Twitch of the cutaneous trunci muscle	Response will be absent caudal to a severe spinal cord lesion. Used to localize lesions between T3 and L3



FIG 63-13
Patellar reflex. The straight patellar ligament is struck, resulting in a reflex "kick" extension of the stifle.

In tense patients the reflex may be decreased or absent in the upper limb but normal in the relaxed recumbent limb.

### Pelvic Limb Withdrawal (Flexor) Reflex

The examiner squeezes a digit with enough pressure to elicit flexion of the hip, stifle, hock, and digits (see Fig. 63-14A and B). If manual pressure is not adequate, the examiner squeezes the base of a toenail with a pair of forceps. The pelvic limb withdrawal reflex is complex. Sensory input is through the peroneal (dorsal, lateral) and tibial (ventral) branches of the sciatic nerve and the saphenous branch of the femoral nerve (medial). Motor output is through the sciatic nerve and its branches, the tibial nerve (digital flexion), and the peroneal nerve (tarsal flexion). Because hip flexion is mediated by the femoral nerve and the lumbar spinal nerves, this reflex can occur when the medial toe is stimulated even if the sciatic nerve and its branches have been destroyed. A decreased pelvic limb withdrawal response indicates an LMN lesion affecting the sciatic nerve (or branches) or the L6-S2 spinal cord segments or nerve roots. A lesion cranial to L6 results in a normal to increased reflex response. The withdrawal response is a segmental reflex that is not dependent on the animal's conscious perception of the noxious stimulus; functional transection of the spinal cord cranial to L6 will result in an increased reflex (UMN) but no ability to feel the stimulus.

### Sciatic Reflex

With the animal in lateral recumbency, the examiner palpates the notch formed by the greater trochanter of the

femur and the ischial tuberosity. Using the tapered end of the pleximeter to tap in this notch, the examiner elicits a brief flexion of the hock (Fig. 63-14C). The sciatic reflex requires that the sciatic nerve, spinal cord segments L6-S2, and the peroneal nerve (branch of the sciatic nerve) be intact. The reflex will be decreased with lesions of those components and normal to increased with UMN lesions cranial to L6.

### Thoracic Limb Withdrawal (Flexor) Reflex

The only reliable forelimb reflex is the withdrawal reflex. Because multiple nerves are involved, this reflex is used as a crude test of the entire brachial plexus (nerve roots and peripheral nerves) and cervical intumescence (C6-T2). The examiner squeezes a digit to elicit flexion of the shoulder, elbow, carpus, and digits (Fig. 63-15). Lesions involving the peripheral nerves, nerve roots, or spinal cord segments at that site will result in a decreased or absent reflex. Lesions above C6 in the spinal cord will cause a normal to increased (UMN) reflex response.

### **Crossed Extensor Reflex**

When the withdrawal (flexor) reflexes are elicited in an animal in lateral recumbency, a reflex extension of the limb opposite the one being stimulated is termed a *crossed extensor reflex*. The presence of this reflex in an animal that is not trying to rise or get away indicates that there is a UMN lesion to the limb being evaluated.

### Perineal Reflex and Bulbourethral Reflex

The perineal and bulbocavernosus reflexes are used to assess the pudendal nerve (sensory and motor) and sacral spinal cord segments S1-S3. In the perineal reflex the perineal skin is pinched with a hemostat, causing the anal sphincter to contract and the tail to ventroflex (Fig. 63-16). The same response should occur during digital rectal examination. The bulbourethral reflex causes anal sphincter contraction in response to gently squeezing the bulb of the penis or the vulva. LMN damage to the pudendal nerve or the S1-S3 spinal cord segments will cause a loss of both of these reflexes, urinary incontinence (LMN bladder), loss of tone in the internal and external anal sphincters, and resultant anal dilation and fecal incontinence.

### **Cutaneous Trunci Reflex (Panniculus)**

Pinching the skin of the dorsum causes a reflex contraction of the cutaneous trunci muscles bilaterally, producing a twitch of the overlying skin. This reflex can be very useful in the evaluation of patients with a severe spinal cord lesion localized to the T3-L3 region. Affected patients will have UMN signs in the rear limbs and normal forelimbs, but unless they have a painful site, it can be difficult to localize the lesion more precisely. When skin along the dorsum is pinched, the stimulated sensory nerve from that site enters the spinal cord and afferent sensory information ascends the spinal cord in sensory tracts. If the spinal cord is intact

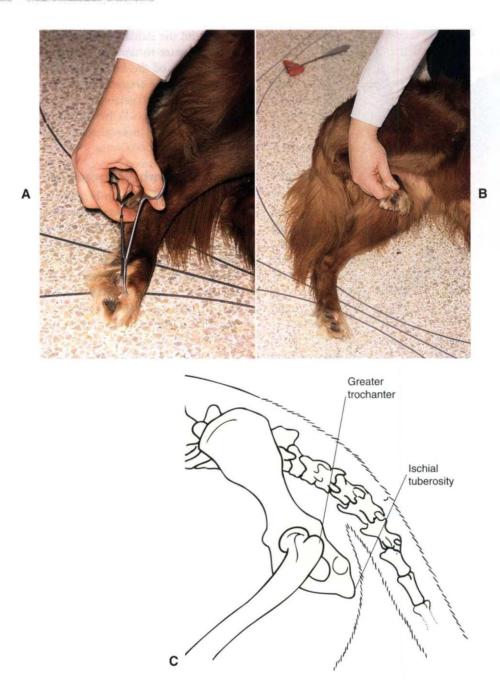


FIG 63-14
Assessing the sciatic nerve and spinal cord segments L6-S2. Pelvic limb withdrawal reflex: Pinch the toe (A), resulting in limb flexion (B). Assess flexion in all of the joints of the limb. It may be necessary to apply a forceps to the nail base to provide adequate stimulation. Sciatic reflex: Strike the sciatic nerve in the notch between the greater trochanter of the femur and the ischial tuberosity, resulting in limb flexion (C).

between the site of stimulation and the C8-T1 segments, a synapse occurs bilaterally at the C8-T1 spinal cord segments, stimulating motor neurons of the lateral thoracic nerve, which causes the cutaneous trunci muscle to contract. In spinal cord lesions causing paralysis the ascending pathway will be disrupted such that no panniculus reflex is elicited when the skin is pinched caudal to the level of the lesion, but stimulation of the skin cranial to the lesion elicits a response (Fig. 63-17). Testing is started at the level of the

ilial wings, although in many normal animals the reflex cannot be elicited until stimulation is applied at the midlumbar region. If a twitch occurs at the most caudal aspect, then the entire pathway is intact. If there is no response, then systematic stimulation of the skin just lateral to each vertebral body should be performed, progressing anteriorly until a twitch is observed. Because the sensory nerves that supply the skin enter the spinal cord one or two vertebrae cranial to the dermatome stimulated, the cord lesion is predictably



FIG 63-15
Thoracic limb withdrawal reflex: Pinch the toe (A), resulting in limb flexion (B). Assess flexion in all the joints of the limb.



FIG 63-16
Perineal reflex: Stimulate the perineal skin with a hemostat, causing the anal sphincter to contract and the tail to ventroflex.

slightly cranial to the site where the panniculus reflex is lost. The cutaneous trunci reflex can be lost unilaterally when there is a lesion of the ipsilateral brachial plexus or C8-T1 spinal cord segments, ventral nerve roots, or spinal nerves. In rare cases this reflex cannot be elicited in a normal dog.

### SENSORY EVALUATION

Evaluation of an animal's ability to feel a noxious stimulus such as a pinch (nociception) can be helpful in the localization of UMN and LMN lesions. When there is a transverse UMN spinal cord lesion, the animal's ability to feel a painful stimulus (skin or pinch with fingers or hemostat) may be decreased in the skin of the trunk and in the limbs caudal to the lesion because the ascending sensory tracts are disrupted in the damaged spinal cord. If minor stimulation (superficial pain assessment) in a paralyzed animal does not elicit a behavioral response such as turning the head, vocalizing, or trying to bite, then the animal's ability to perceive a more severe noxious stimulus such as a hemostat applied to the nail base (deep pain) should be tested. The spinal tracts that carry deep pain sensation are small, bilateral, and multisynaptic and located deep in the spinal cord white matter. Only a very severe bilateral spinal cord lesion will completely disrupt these tracts, making the ability to perceive deep pain an important prognostic indicator in animals with severe spinal cord injury (Fig. 63-18). It is important to remember that withdrawal of the limb indicates only an intact reflex arc (peripheral nerve and spinal cord segments), whereas a behavioral response requires that the sensory spinal cord tracts ascending to the brain also be intact.

When LMN paralysis of a limb is evident, mapping the boundaries of normal and diminished sensation can aid in lesion localization to specific peripheral nerves, dorsal nerve roots, or spinal cord segments. The skin should be pinched with a hemostat and regions of local anesthesia or decreased sensation identified (Fig. 63-19). These results can be compared with established maps of cutaneous regions deriving sensory innervation from individual nerves (dermatomes), allowing the LMN neurologic defect to be precisely localized (see Chapter 73).

### PAIN/HYPERPATHIA

The neck, spine, limbs, muscles, bones, and joints should be palpated and manipulated to detect painful areas or restricted mobility. Pain is usually most intense directly over a lesion, making this part of the neurologic examination important in lesion localization. Traumatic and inflammatory conditions are most likely to be painful, whereas degenerative and congenital conditions are rarely painful. Neoplastic condi-

FIG 63-17

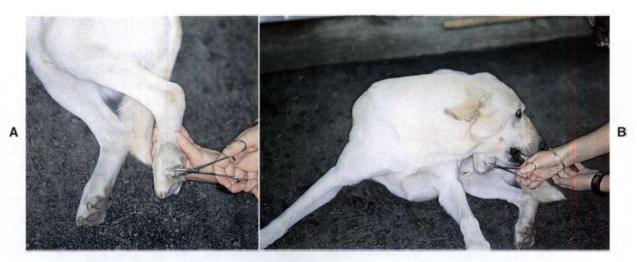
Cutaneous trunci reflex.  $\bf A$  and  $\bf B$ , Pinch the dorsal skin with a hemostat just lateral to the spine. If the spinal cord is not injured between the site of stimulation and the C8-T1 spinal cord segments, this will lead to a bilateral twitch of the cutaneous trunci muscle. The reflex may be absent caudal to a severe spinal cord lesion.  $\bf C$ , The spinal sensory nerves course caudally so that the dermatomes for skin sensation lateral to the vertebral column are caudal to their own vertebral bodies. A spinal cord lesion at site a will therefore result in loss of the panniculus response caudal to site b.

tions causing distortion of tissues (meninges, nerve roots, or bone) will also be painful.

The animal's posture and gait should be observed. Animals with neck pain maintain a low head carriage, with their head and neck extended, and are unwilling to turn their neck to

look to the side; they will instead pivot their entire body. Animals with pain of the thoracic or lumbar spine stand with an arched back (Fig. 63-20). Animals with painful bones, joints, or muscles typically have a short-strided, stiff gait and are reluctant to exercise.





**FIG 63-18**Evaluation of deep pain. Pinch the toe **(A)** to assess whether this elicits a behavioral response **(B).** The absence of deep pain sensation indicates the presence of severe spinal cord damage.



FIG 63-19
Sensory loss in the dorsolateral foot (A) and distal rear limb (B) in a lemur after damage to the peroneal nerve by an intramuscular injection.

Neck pain is a sign commonly associated with compressive or inflammatory diseases of the cervical spinal cord, cervical spinal roots, or meninges. The neck should be gently manipulated in dorsal, lateral, and ventral flexion and resistance to movement or pain assessed. Deep palpation of the vertebrae and cervical spinal epaxial muscles may also be performed (Fig. 63-21). Anatomic structures that can cause neck pain include the meninges, nerve roots, intervertebral disks, facetal joints, bones, and muscles (Box 63-8). Neck pain has also been recognized as a clinical symptom of intracranial disease, particularly of forebrain mass lesions.

Pain in other regions of the vertebral column may help localize lesions caused by intervertebral disk disease, diskospondylitis, or neoplasia. Dogs and cats with disease of the thoracolumbar spine may experience pain when pressure is applied over the affected vertebrae. Because these animals may also resist abdominal palpation, vertebral or spinal hyperpathia may be misinterpreted as abdominal pain. Cauda equina compression that is caused by a tumor, disk, or ligamentous proliferation typically causes pain in the lumbosacral region (see Chapter 70). This can be demonstrated in affected dogs by applying direct pressure over the lumbosa-



FIG 63-20

This 1-year-old Boxer stands with an arched back because of pain associated with diskospondylitis.



BOX 63-8

Causes of Neck Pain

### Muscle

Polymyositis (immune, infectious) Muscle injury

### Rone

Fracture/luxation Atlantoaxial instability/subluxation Diskospondylitis/osteomyelitis Wobbler syndrome Neoplasia

### Joint (Facetal Joints)

Polyarthritis (immune, infectious) Degenerative joint disease (osteoarthritis)

### Intervertebral Disk

Disk degeneration/prolapse (pain due to nerve root or meningeal compression)

### **Nerve Root**

Neoplasia

Compression (by disk, tumor, fibrous tissue, arachnoid cysts)

### Meninges

Neoplasia

Infectious meningitis/meningomyelitis Granulomatous meningoencephalitis (GME) Steroid responsive meningitis arteritis (aseptic meningitis) Hemorrhage-induced inflammation

### **Brain**

Mass lesion (neoplasia, inflammatory)

cral junction or applying dorsal traction to the tail (see Fig. 70-20).

Muscular pain should be assessed by manipulating the limbs and palpating individual muscle groups. During palpation it is important to attempt to differentiate pain that originates within the muscle from that caused by bone or joint abnormalities. Muscle disorders that are associated with pain are primarily the inflammatory diseases, such as immune-mediated polymyositis, masticatory myositis, and infectious myositis caused by the protozoal organisms Toxoplasma and Neospora. Ischemic myopathy, as occurs in animals with thrombosis affecting the arterial blood supply to a muscle group, can also result in severe muscular cramping and pain on palpation.

### URINARY TRACT FUNCTION

Severe lesions of the spinal cord are often associated with urinary tract dysfunction. Bladder function should be assessed on the basis of the owner's or the clinician's observations of micturition, palpation of the bladder, and attempts to express urine. A flaccid, easily expressed bladder with absent or diminished perineal and bulbocavernosus reflexes and reduced anal tone is expected with lesions of the LMN (S1-S3 spinal cord segments, pudendal nerve, pelvic nerve). UMN lesions cranial to the sacral segments cause diminished voluntary control of urination and reflex hyperexcitability of the urethral sphincter. There can be incomplete voiding or detrussor-urethral dyssynergia. Severe UMN lesions will result in a tense distended bladder that is difficult to express.

### **CRANIAL NERVES**

Cranial nerve dysfunction may result from a disorder affecting a single nerve; a diffuse polyneuropathy affecting multiple nerves; or a cluster of abnormalities, as is commonly seen in animals with a disease affecting the middle and inner ear or the brainstem. Animals with brainstem disease causing cranial nerve dysfunction usually have additional signs such as postural reaction deficits, hemiparesis, quadriparesis or altered mentation.

Cranial nerve examination is not difficult. The cranial nerves that are most often affected can be evaluated quickly with a rapid regional neurologic examination (Table 63-5). If findings yielded by the preliminary examination indicate the presence of an abnormality, a more thorough examination of each individual cranial nerve can be undertaken (Table 63-6; see also Suggested Readings).

### **Evaluation of Menace Response, Vision,** and Pupils

The optic nerve (CN1) is an important component of the afferent pathways for the menace response, vision, and the pupillary light reflex. The examiner covers one eye and assesses the menace response in the opposite eye. Next, the examiner advances a hand or finger toward the eye being evaluated, taking care to avoid touching the eyelid or whiskers or generating an air current that will stimulate the

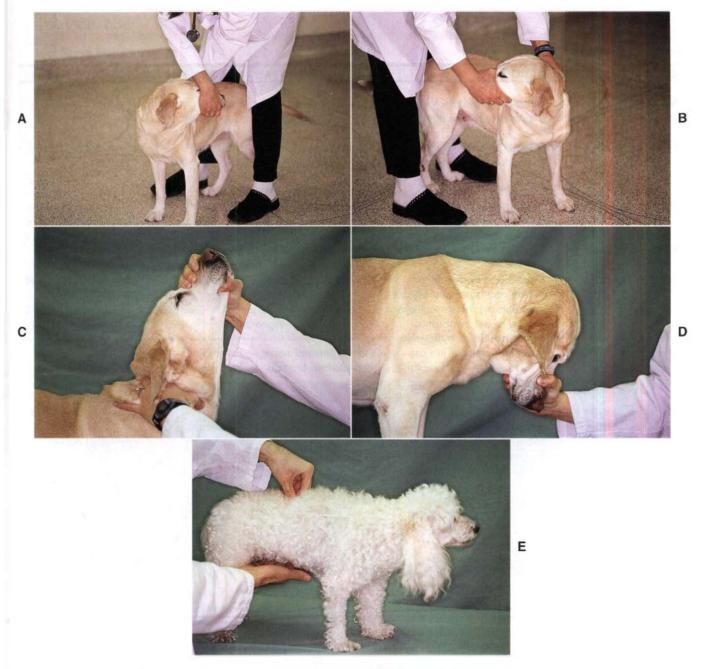


FIG 63-21
Testing for cervical and thoracolumbar spinal pain by (A to D) manipulating the neck through a full range of motion and (E) applying pressure through deep palpation of the vertebral bodies and spinal epaxial muscles.

cornea, which is innervated by the sensory portion of the trigeminal nerve (CN5). The menace response is a learned response and will not be present until 10 to 12 weeks of age in puppies and kittens. In addition to the menace response, the examiner should observe the animal's response to its environment by making sudden movements and dropping cotton balls to see if the animal follows the movement. It may be necessary to set up a maze of objects to assess vision in each eye. Pupil size should be examined at rest in a well-

lighted room and then in a dimly lit room and the two eyes compared. The examiner evaluates the ability of each pupil to constrict (parasympathetic function) and to dilate (sympathetic function) by shining a bright light in one eye, then swinging the light into the other eye to observe the response, and then swinging it back again. The parasympathetic axons of the oculomotor nerve (CN3) are responsible for pupil constriction. Loss of vision and pupillary abnormalities are discussed in Chapter 66.



TABLE 63-5

### Regional Assessment of Cranial Nerves

CRANIAL NERVE TEST	ACTION	SENSORY INPUT	INTEGRATION	MOTOR FUNCTION
Menace response	Threatening gesture towards eye; results in a blink	CN2-optic nerve	Forebrain Cerebellum Brainstem	CN7—facial nerve
Palpebral reflex	Touching medial or lateral canthus of eye results in blink	CN5—trigeminal nerve medial: ophthalmic branch	Brainstem	CN7—facial nerve
Pupillary light reflex	Shining a light in the eye elicits pupillary constriction	lateral: maxillary branch CN2—optic nerve	Brainstem	CN3—oculomotor nerve (parasympathetic)
Examine for head tilt	Evaluate head position	CN8-vestibulocochlear	Brainstem Cerebellum	_
Vestibulo-ocular reflex	Move head from side to side and dorsoventrally, evaluating for normal eye movements, strabismus and positional nystagmus	CN8vestibulocochlear	Brainstem	CN3—oculomotor nerve CN4—trochlear nerve CN6—abducent nerve
Stimulation of nasal mucosa	Inserting hemostat in nose to stimulate nasal septal mucosa; results in rapid withdrawal of head	CN5—trigeminal nerve (ophthalmic branch)	Forebrain Brainstem	_
Jaw tone	Assess jaw tone and ability to close the mouth	CN5—trigeminal nerve (mandibular branch)	Forebrain Brainstem	CN5—trigeminal nerve
Facial symmetry	Examine for facial symmetry, ability to blink, twitch lip, and move ears	CN2—optic nerve (menace) CN5—trigeminal nerve (palpebral, corneal reflex, lip pinch)	Forebrain Brainstem	CN7—facial nerve
Gag reflex	Manual stimulation of the pharynx induces contraction	CN9— glossopharyngeal CN10—vagus nerve	Brainstem	CN9—glossopharyngeal nerve CN10—vagus nerve
Tongue evaluation	Inspect the tongue for symmetry, observe tongue movements during eating and drinking	CN5—trigeminal nerve CN7—facial nerve CN12—hypoglossal nerve	Brainstem	CN12—hypoglossal nerve

# Examine for Strabismus, Nystagmus, and Head tilt

To check for strabismus, nystagmus, and head tilt, the examiner must determine whether the eyes are normally positioned in the orbits and whether there is any abnormal resting (spontaneous) nystagmus. Spontaneous nystagmus indicates either a central vestibular (medullary) lesion, a lesion of the vestibular portion of CN8, or a lesion of the cerebellum. A head tilt is common with a lesion in any of these locations. Abnormal eye position (strabismus) may indicate a vestibular disorder or damage to the innervation of the extraocular muscles (CN3, 4, 6) (Fig. 63-22). Oculomotor nerve (CN3) dysfunction can result in a ventrolateral strabismus and an inability to rotate the eye dorsally, ventrally, or medially. Lesions of the abducent (CN6) nerve cause a medial strabismus and an inability to look laterally,

and lesions of the trochlear nerve (CN4) cause a dorsolateral rotation of the eye. Lesions of these nerves (CN3, 4, 6) usually occur together, producing complete external ophthalmoplegia. Vestibular disorders commonly cause a ventral strabismus (eye drop) on the side of the lesion that may be evident only during head and neck extension. A quick assessment of the function of all these nerves can be accomplished by moving the head from side to side and eliciting the vestibulo-ocular reflex. As the head is turned slowly to the right, the gaze of both eyes should slowly drift left before jerking to the right to resume a central position. The examiner assesses these normal vestibular eye movements (physiologic nystagmus) while moving the head in each direction.

In addition to moving the head from side to side to determine whether the eye movements are normal, the examiner should hold the animal's head still in each lateral position to



TABLE 63-6

### Cranial Nerve Function

CRANIAL NERVE	SIGNS OF LOSS OF FUNCTION
I (olfactory)	Loss of ability to smell
II (optic)	Loss of vision, dilated pupil, loss of pupillary light reflex (direct and consensual when light shone in affected eye)
III (oculomotor)	Loss of pupillary light reflex on affected side (even if light shone in opposite eye), dilated pupil, ventrolateral strabismus
IV (trochlear)	Slight dorsomedial eye rotation
V (trigeminal)	Atrophy of temporalis and masseter muscles, loss of jaw tone and strength, dropped jaw (if bilateral), analgesia of innervated areas (face, eyelids, cornea, nasal mucosa)
VI (abducent)	Medial strabismus, impaired lateral gaze, poor retraction of globe
VII (facial)	Lip, eyelid, and ear droop; loss of ability to blink; loss of ability to retract lip; possibly decreased tear production
VIII (vestibulocochlear)	Ataxia, head tilt, nystagmus, deafness
IX (glossopharyngeal)	Loss of gag reflex, dysphagia
X (vagus)	Loss of gag reflex, laryngeal paralysis, dysphagia
XI (accessory)	Atrophy of trapezius, sternocephalicus, and brachiocephalicus muscles
XII (hypoglossal)	Loss of tongue strength



FIG 63-22
Head tilt (A) and ventrolateral strabismus (B) in a 2-year-old Dachshund after needle trauma to the brainstem during cervical myelography.

determine whether an abnormal (positional) nystagmus develops. The head and neck should then be extended and held in that position while the eyes are evaluated for a ventral strabismus and the development of nystagmus. When the head of a normal animal is held still, there will be no nystagmus. In most animals with severe or acute central or peripheral vestibular lesions, there will be a resting (spontaneous) nystagmus regardless of the position of the head. In less severe or compensated vestibular disorders the examiner will be able to elicit only a few beats of abnormal nystagmus when the animal's head is held in a certain position; this is called positional nystagmus, and it is abnormal. Positional nystagmus will sometimes be evident only when the animal is placed in dorsal recumbency with the head and neck extended (Fig. 63-23). The direction of nystagmus is defined as the direction of the fast phase of eye movements.

### **Evaluation of Trigeminal (CN5) Nerves**

The trigeminal nerve (ophthalmic and maxillary branches) supplies the sensory innervation to the skin of the face, the cornea, the mucosa of the nasal septum, the nasopharyngeal mucous membranes, and the teeth and gingiva of the upper jaw. The mandibular branch supplies sensory innervation to the mandibular portion of the face and oral cavity as well as motor function to the muscles of mastication. Sensory function is tested by assessing the corneal and palpebral reflexes, assessing the response to stimulation of the nasal septal mucosa, and pinching the skin of the face with a hemostat (Fig. 63-24). Motor function is assessed by evaluating the size and symmetry of the masticatory muscles and testing the resistance of the jaw when opening the mouth. Bilateral trigeminal motor paralysis results in a dropped jaw and inability to close the mouth (Fig. 63-25). Loss of corneal sensation

will decrease reflex release of tears and trophic factors, leading to keratitis (neurotrophic keratitis) and corneal ulceration in some dogs.

### **Evaluation of the Facial Nerves (CN7)**

The facial nerve provides motor innervation to the muscles of the face and sensory innervation to the rostral two thirds of the tongue (for taste) and palate. Parasympathetic fibers innervate the lacrimal glands and the mandibular and sublingual salivary glands and can be assessed with a Shirmer tear test. Motor function is assessed by examining the face for symmetry and observing spontaneous blinking and ear movements as well as by eliciting the corneal and palpebral reflexes, the menace response, and the ability to twitch the face in response to a pinch (sensory CN5). Because the facial nerve courses through the middle ear before distribu-



**FIG 63-23**Placing an animal in dorsal recumbency can reveal positional nystagmus or strabismus.

tion to the muscles of the face, middle ear lesions can cause dysfunction.

# Evaluation of the Glossopharyngeal (CN9), Vagus (CN10), and Hypoglossal (CN12) Nerves

The glossopharyngeal, vagus, and hypoglossal nerves are usually evaluated together as components of the gag reflex and normal eating and drinking. The glossopharyngeal nerve (CN9) provides motor innervation to the pharynx and palate and sensory innervation to the caudal third of the tongue and pharynx. It also provides parasympathetic stimulation to the parotid and zygomatic salivary glands. The vagus nerve (CN10) provides motor and sensory innervation to the larynx, pharynx, and esophagus and sensory innervation to the thoracic and abdominal viscera. The parasympathetic portion of the vagus provides motor innervation to most thoracic and abdominal viscera. The hypoglossal nerve (CN12) provides motor innervation to the tongue.

The swallowing or gag reflex (CN9 and CN10) can be evaluated by applying external pressure in the hyoid region to induce swallowing or by stimulating the pharynx with a finger to induce the gag reflex. This can also be evaluated by watching the animal eat and drink. The parasympathetic portion of CN10 can be tested by measuring the reflex bradycardia that normally occurs when applying digital pressure to both eyeballs (oculocardiac reflex). The hypoglossal nerve (CN12) can be evaluated by inspecting the tongue for atrophy or asymmetry (Fig. 63-26) and observing tongue movement during eating and drinking or when licking food paste placed on the nose.

### **LESION LOCALIZATION**

After the neurologic examination is completed, an animal's mentation, cranial nerves, posture, gait, forelimbs, rear limbs, perineum, anus, and bladder can be characterized as normal



FIG 63-24
The sensory distribution of the trigeminal nerve (CN5) can be assessed by pinching the skin of the maxilla (A) and by stimulating the nasal septal mucosa (B) with a hemostat.



FIG 63-25
Bilateral motor paralysis of the trigeminal nerve results in an inability of this 6-year-old Labrador Retriever to close its mouth.



**FIG 63-26**Deviation and atrophy of the tongue caused by left-sided hypoglossal nerve (CN12) paralysis.

or abnormal. If disease above the foramen magnum is present, clinical findings should allow a lesion to be localized to a specific region of the brain. In patients with spinal cord disease determining whether the neurologic abnormality in each limb is UMN or LMN in origin allows localization to a region of the spinal cord or specific spinal cord segments (see Box 63-4). When LMN signs are present in a single limb, the lesion can often be even more precisely localized by determining the muscles affected and, if sensory nerves are also affected, by testing sensation in dermatomes. Focal hyperpathia may also help to precisely localize a lesion. Whenever possible, the clinician should be able to explain all detected neurologic abnormalities on the basis of a single lesion. Occasionally, however, this will be impossible because the animal has multiple foci of disease or a diffuse disorder.



### BOX 63-9

### DAMNIT-VP Scheme: Mechanisms of Disease

- **D** Degenerative
- A Anomalous
- M Metabolic, malformation
- N Neoplastic, nutritional
- Infectious, inflammatory, immune, iatrogenic, idiopathic
- T Traumatic, toxic
- V Vascular
- P Parasitic

### DIAGNOSTIC APPROACH

Once a neurologic lesion has been localized, it is necessary to generate a list of likely differential diagnoses. This list should take into account the signalment, historical data, the neuroanatomic location of the lesion, and the nature of the onset and progression of neurologic signs. It is important to consider all possible mechanisms or causes of disease that can affect the nervous system (Box 63-9). Once a list of likely differential diagnoses has been developed, diagnostic tests can be performed to confirm or exclude each.

### **ANIMAL HISTORY**

Patient age, gender, breed, and lifestyle may provide clues regarding the underlying disease. Young animals are most likely to be seen because of congenital or hereditary disorders; they are also at highest risk for intoxications and infectious diseases. Older animals are more susceptible to neoplastic diseases and many of the known degenerative disorders. Certain breeds are predisposed to particular disorders, and there are many congenital and inherited disorders that have been seen in only one or a few breeds. Dogs engaging in particular competitive or working activities (e.g., hunting, herding, racing, jumping) may be at increased risk for specific activity-related injuries. Potential exposure to trauma, toxins, and infectious disorders should be ascertained through careful history taking.

### **DISEASE ONSET AND PROGRESSION**

Evaluation of the onset and progression of neurologic signs is of primary importance in prioritizing the list of differential diagnoses (Box 63-10). The signs may be peracute and nonprogressive, or they may become progressively more severe with time. In peracute disorders the time of onset of the neurologic signs can be pinpointed exactly, with the animal going from being normal to abnormal within minutes or hours. Signs reach maximal intensity very rapidly and then remain static or improve over time. Examples include external trauma, internal trauma from intervertebral disk extrusion, vascular disorders such as infarcts or hemorrhage, and some rapid-acting intoxications such as strychnine. Rarely, animals with a typically slowly progressive disorder such as a tumor present with a peracute exacerbation of their



BOX 63-10

Characterization of Disease Processes Based on Onset and Progression

### Peracute (Minutes to Hours)

External trauma
Hemorrhage
Infarct
Internal trauma (disk extrusion, fracture)

Some intoxications

### Subacute Progressive (Days to Weeks)

Infectious disease
Noninfectious inflammatory disease
Rapidly growing tumors (lymphoma, metastatic neoplasia)
Metabolic disorders
Some intoxications

### **Chronic Progressive (Months)**

Most tumors Degenerative disorders

signs as a result of hemorrhage or fracture at the site of the tumor. A thorough history will often reveal that these animals were not entirely normal before the acute deterioration.

Neurologic disorders with fairly rapid deterioration over days to weeks are classified as subacute and progressive. Infectious and noninfectious inflammatory diseases and some of the more rapidly progressive neoplasms (e.g., lymphomas, metastatic malignancies) usually fall into this category. Metabolic and nutritional disorders and some intoxications can also cause subacute progressive signs. Animals with chronic progressive signs that develop very slowly over many weeks or months are most likely to have neoplastic or degenerative disease.

### SYSTEMIC SIGNS

Identification of concurrent systemic abnormalities may aid in the diagnosis of neoplastic, metabolic, or inflammatory nervous system disorders. A complete physical examination and ophthalmologic evaluation, including a funduscopic examination, should be performed in every animal with suspected neurologic disease. Laboratory tests and imaging modalities useful for specific evaluation of nervous system disorders are limited, so identification and characterization of associated abnormalities in other tissues can facilitate diagnosis. Ancillary diagnostic tests can then be performed to further evaluate animals with neurologic disease and thereby arrive at a specific diagnosis.

### Suggested Readings

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# CHAPTER Diagnostic Tests for the Neuromuscular System

### CHAPTER OUTLINE

MINIMUM DATABASE OTHER ROUTINE LABORATORY TESTS IMMUNOLOGY, SEROLOGY, AND MICROBIOLOGY RADIOGRAPHY

Radiographs

CEREBROSPINAL FLUID COLLECTION AND

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**Analysis** 

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Computed Tomography and Magnetic Resonance

**Imaging** 

**ELECTRODIAGNOSTIC TESTING** 

Electromyography

Nerve Conduction Velocities

Electroretinography

Brainstem Auditory Evoked Response

Electroencephalography

BIOPSY OF MUSCLE AND NERVE

Muscle Biopsy

Nerve Biopsy

### MINIMUM DATABASE

Patients with disease confined to the central nervous system (CNS) often have no specific abnormalities on a minimum database consisting of a complete blood cell (CBC) count, serum biochemistry profile, and urinalysis. These tests can be useful, however, in the diagnosis of systemic disorders that have neurologic manifestations and in the identification

of the clinicopathologic abnormalities associated with some primary neurologic disorders.

Hematologic findings are rarely specific, but leukocytosis suggests inflammatory disease. Severe inflammation and a left shift are expected in patients with bacterial meningitis or encephalitis. Lymphopenia and inclusion bodies within red blood cells (RBCs) and lymphocytes are occasionally seen in dogs with acute canine distemper virus infection. Morulae may be seen within neutrophils in dogs with granulocytic ehrlichiosis. Microcytosis with or without thrombocytopenia is a common finding in dogs with portosystemic shunts. Red cell regeneration with or without accompanying anemia is seen in dogs with recurrent intraperitoneal hemorrhage caused by abdominal hemangiosarcoma. Occasionally, concurrent leukemia is detected in an animal with brain or spinal cord lymphoma.

A serum biochemistry profile is most useful in determining the likelihood of metabolic disorders as the cause of neuropathies, encephalopathies, and seizures. Diabetes mellitus, hypoglycemia, hypocalcemia, hypokalemia, and uremia can be eliminated from the list of differential diagnoses if the biochemistry panel is found to be normal. In dogs with peripheral neuropathy and a greatly increased serum cholesterol concentration, diagnostic tests for hypothyroidism should be considered (see Chapter 51). The finding of high liver enzyme activities (i.e., alanine aminotransaminase, serum alkaline phosphatase) or hypoalbuminemia in a patient with forebrain signs should prompt consideration of liver function tests to rule out hepatic encephalopathy (see Chapter 36). Hepatocellular enzyme elevations are also expected with some multisystemic disorders, such as toxoplasmosis and metastatic neoplasia. Serum creatine kinase is elevated in dogs and cats with muscle inflammation or necrosis. Urine specific gravity differentiates primary renal from prerenal azotemia. Hypernatremia is common when animals stop drinking or develop diabetes insipidus because of intracranial disease. Extremes of hyponatremia and hypernatremia and rapid correction of sodium imbalances cause brain dysfunction (see Chapter 55). Ammonium biurate crystals are occasionally found in the urine of dogs and cats with portosystemic shunts.

### **OTHER ROUTINE LABORATORY TESTS**

Additional biochemical tests are frequently performed during the diagnostic evaluation of patients with neurologic disorders. Preprandial and postprandial bile acids are routinely measured to rule out hepatic encephalopathy in animals with forebrain signs and to monitor liver function in animals being chronically treated with some anticonvulsants. Alternatively, provocative ammonia tolerance testing can be used to assess hepatic function in nonencephalopathic patients, and resting ammonia concentration can be measured in encephalopathic patients. Serum concentrations of anticonvulsants are routinely monitored (see Chapter 67). Whenever CNS hemorrhage is considered as a possible differential diagnosis, coagulation should be assessed by determining either the activated clotting time (ACT) or the prothrombin time (PT) and partial thromboplastin time (PTT). When abnormalities of calcium or glucose regulation are detected on the minimum database, further endocrinologic testing is recommended. Specific endocrine testing is also warranted when thyroid disease, hypoadrenocorticism, or hyperadrenocorticism could be responsible for an animal's neurologic signs.

### IMMUNOLOGY, SEROLOGY, AND MICROBIOLOGY

A number of special diagnostic tests can be performed in patients with neurologic disorders when infectious or immune-mediated diagnoses are being considered. Clinicians should routinely perform bacterial culture of the cerebrospinal fluid (CSF), blood, and urine in patients with inflammatory disease of the brain, spinal cord, or meninges. Concurrent systemic illness, potential for exposure, and vaccination status will determine what additional testing is warranted. When lesions outside of the CNS are identified, such as pneumonia or dermatitis, the most direct route to a diagnosis is usually by sampling those sites. Serum antibody or antigen tests are also available for many of the infectious agents that can affect the CNS. An increased titer of specific antibody in CSF relative to that in serum may be required to make a definitive diagnosis. Alternatively, immunohistochemical staining can be used to identify organisms in tissue (brain, spinal cord, or muscle). In some cases polymerase chain reaction (PCR) analysis is available for diagnosis of active infection by a specific organism.

Immune-mediated CNS disorders such as steroidresponsive meningitis-arteritis (SRMA) and granulomatous meningoencephalomyelitis (GME) are relatively common in dogs. Diagnosis requires finding typical clinical and clinicopathologic abnormalities and eliminating the possibility of infectious disorders, as previously. Dogs with SRMA commonly have elevated scrum and CSF IgA levels, and some have concurrent immune-mediated polyarthritis, which contributes to the diagnosis. In dogs with polyneuropathies, polymyositis, or apparent multisystemic immune-mediated

disease, it may be useful to measure antinuclear antibody (ANA) titers to support a diagnosis of systemic lupus erythematosus (SLE). Most dogs with acquired myasthenia gravis have detectable circulating antibodies against acetylcholine receptors, and some dogs with masticatory muscle myositis have serum antibodies directed against type 2M myofibers (See Chapter 72).

### RADIOGRAPHY

### RADIOGRAPHS

Radiographs of the thorax and abdomen can be useful as screening tests for infectious and neoplastic diseases and as a means of evaluating liver size. These are noninvasive tests that should be performed routinely.

Spinal radiographs are necessary and useful in the diagnosis of congenital malformations, fractures and luxations, disk disease, diskospondylitis, and primary or metastatic vertebral neoplasia. In most cases general anesthesia is required to obtain lateral and ventrodorsal radiographs of sufficient quality to permit the detection of subtle abnormalities. Radiographs should be centered on the region of clinical interest as established by the neurologic examination. Neoplasia of the soft tissues of the brain or spinal cord generally does not cause radiographic abnormalities. Although skull radiographs are a low-yield procedure, they are often performed in animals with disease above the foramen magnum, because finding an area of lysis, a region of tumor calcification, or an intranasal mass aids in diagnosis.

### CEREBROSPINAL FLUID COLLECTION AND ANALYSIS

### INDICATIONS

Analysis of CSF can be useful in the diagnostic evaluation of patients with CNS disease. Specific neurologic disorders often cause typical alterations in CSF cytology or protein concentration, aiding diagnosis. In addition, special techniques such as bacterial culture, organism identification, antibody determination, and PCR can be performed on CSF, leading to a definitive diagnosis in some patients with infectious CNS disease. CSF examination is indicated in most animals with certain or suspected neurologic disease in which a diagnosis is not readily apparent, once traumatic, metabolic, and congenital abnormalities have been excluded. Analysis of CSF is most likely to be diagnostic in dogs and cats with intracranial lesions causing progressive forebrain signs and in animals with fever and axial pain. In animals with evidence of spinal cord disease, CSF analysis should always be performed before myelography to rule out inflammatory disease.

### CONTRAINDICATIONS

If the proper technique is followed, the procedure for obtaining CSF is safe and simple. The animal is first placed under



BOX 64-1

### Signs Suggesting Increased Intracranial Pressure

Depressed mentation or abnormal behavior Constricted, dilated, or unresponsive pupils Bradycardia Increased arterial blood pressure Altered breathing pattern



BOX 64-2

### Treatment Steps to Decrease Intracranial Pressure

Oxygenate

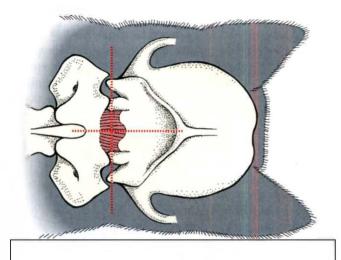
Administer 20% mannitol: 1.0 g/kg, administered intravenously over 15 minutes

Furosemide: 1 mg/kg, administered intravenously

If anesthesia is necessary:

Rapid induction, intubate, and ventilate to maintain PaCO<sub>2</sub>

30-40 mmHg



### FIG 64-1

Landmarks for cerebrospinal fluid (CSF) collection at the cerebellomedullary cistern. The site of needle entry is at the intersection of the dorsal midline and the most cranial aspect of the wings of the atlas.

general anesthesia, and the puncture site is prepared in a sterile fashion, thereby minimizing the risk of damage resulting from animal movement and the risk of iatrogenic infections. Spinal puncture should not be performed in an animal that is an obvious anesthetic risk or that has a severe coagulopathy. General anesthesia and collection of CSF should not be performed in any patient with suspected increased intracranial pressure (Box 64-1) without first taking steps to lower the intracranial pressure in order to decrease the risk of brain herniation (Box 64-2).

### **TECHNIQUE**

In dogs and cats the most reliable source of CSF for analysis is the cerebellomedullary cistern. The L5-L6 site may also be used, but it is more difficult to obtain a large volume of uncontaminated fluid from this site. Although it has been stated that CSF obtained from the cerebellomedullary cistern best reflects the nature of intracranial disease, whereas fluid from a lumbar tap is more useful in characterizing spinal cord disease, diagnostically the two are not significantly different. Lumbar CSF from normal dogs may have a slightly higher protein content and lower nucleated cell count than CSF obtained from the cerebellomedullary cistern.

### **Cisternal Puncture**

With the animal under general anesthesia, the clinician should prepare the back of its neck between the ears from the occipital protuberance to C2 for surgery. If the clinician is right-handed, the animal should be placed in right lateral recumbency with its neck flexed so that the median axis of the head is perpendicular to the spine. The nose should be elevated slightly so that its midline is parallel to the surface of the table. With the thumb and third finger of the left hand,

the clinician should palpate the cranial edges of the wings of the atlas and draw an imaginary line at their most cranial aspect.

The examiner can then use the left index finger to palpate the external occipital protuberance and draw a second imaginary line caudally from that site along the dorsal midline. The needle should be inserted where the two imaginary lines intersect (Fig. 64-1).

A 1<sup>1</sup>/<sub>2</sub>- or 3-inch (3.75 to 7.5 cm) long styletted spinal needle is then directed straight in through the skin, perpendicular to the spine, and into the underlying tissues. The needle is advanced 1 to 2 mm at a time, and the stylette is removed so that the clinician can look for CSF fluid. While the right hand is used to remove the stylette, the thumb and first finger of the left hand, which is rested against the spine for support, should grasp and stabilize the hub of the needle. A sudden "pop" may be felt as the dorsal atlantooccipital membrane and the dura mater and arachnoid mater are penetrated simultaneously (Fig. 64-2). This is not a reliable sign, however, and the level at which the subarachnoid space is reached varies greatly with the breed and individual animal. It is often very close to the skin surface in toy breeds and some cats.

If the needle strikes bone, it should be withdrawn, the patient position and landmarks reassessed, and the procedure repeated. If whole blood appears in the spinal needle, the needle should be withdrawn and the procedure repeated with another sterile needle. When CSF is observed, the fluid should be allowed to drip directly from the needle into a test tube. The clinician should check with the laboratory to determine the type of tube preferred for collection of CSF. The amount of CSF collected ranges from 0.5 to 3 ml depending on the size of the animal. Simultaneous jugular vein

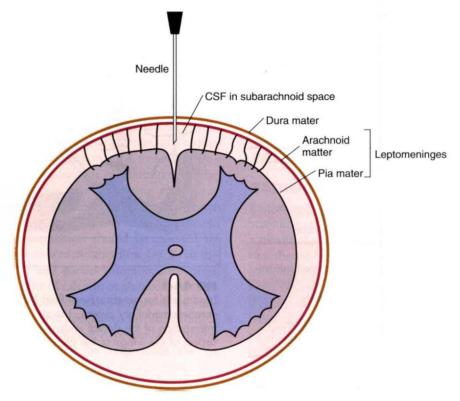
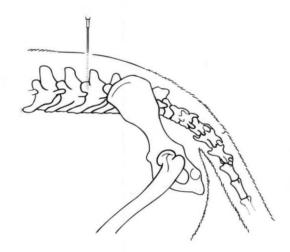


FIG 64-2
Transverse section showing the relationship among the meninges, the cerebrospinal fluid (CSF), and the spinal cord. The tip of the needle is in the subarachnoid space, as it would be for CSF collection or myelography.

compression may hasten flow but will transiently increase intracranial pressure. Blood in the CSF may be the result of the disease or of the tap. If it is caused by the procedure, the amount of blood should decrease as the CSF drips from the needle. If this occurs, some of the less contaminated fluid should be collected in a second tube for cytologic evaluation. Mild CSF contamination with hemorrhage (<500 RBCs/µl) does not alter the CSF protein and leukocyte determinations. Grossly hemorrhagic CSF should always be collected into a tube containing ethylenediaminetetraacetic acid (EDTA) to prevent clotting.

### **Lumbar Puncture**

The animal is placed in lateral recumbency with its trunk flexed. Foam cushions are placed between its limbs and beneath the lumbar region to achieve true lateral positioning. A 3<sup>1</sup>/ -inch (8.75-cm) spinal needle is inserted on midline at the cranial edge of the dorsal spinal process of the L5 or L6 vertebra and directed ventrally into the ligamentum flavum (Fig. 64-3). The needle is passed in a smooth motion through or alongside the caudal spinal cord and cauda equina into the ventral subarachnoid space. The animal's tail and pelvic limbs may twitch when the cord is penetrated. Because CSF flow is slower from this site and more likely to be contaminated by blood, cerebellomedullary collection is usually preferred for diagnostic purposes.



Landmarks for cerebrospinal fluid (CSF) collection from a lumbar site. The needle is inserted at the cranial edge of the dorsal spinal process of the L6 vertebra.

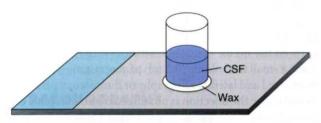
### **ANALYSIS**

Normal CSF is clear and colorless. A cell count should be performed and a cytologic preparation made for examination as soon as possible because white blood cells (WBCs) in the CSF deteriorate rapidly. If the sample must be stored

for longer than 1 hour before analysis, the specimen should be refrigerated to slow cellular degeneration. The addition of autologous serum (10% by volume of the sample) will preserve CSF so that cytologic analysis 24 to 48 hours after collection will yield reliable results, but a separate sample must be saved for protein analysis. Alternatively, one drop of buffered 10% formalin can be added for each 0.25 ml of CSF to preserve cytologic features without affecting the protein measurement.

Once the fluid is collected, a total cell count is performed and the concentration of RBCs and WBCs is determined. The normal range of values varies with each laboratory, but in general there should be fewer than five WBCs per microliter. An increased number of CSF WBCs is referred to as *a pleocytosis*. A pleocytosis should be further characterized by microscopic examination and differential cell count to determine the predominant leucocyte present. Cytologic analysis of CSF is necessary even if the WBC count is normal because there may be abnormal cell types or organisms present.

A concentration procedure is usually required to obtain sufficient cells for cytologic assessment if the CSF WBC count is less than 500 cells/µl. Cytocentrifuge concentration of CSF is available in most institutions and commercial laboratories, and results are best if samples are processed within 30 minutes of collection or if samples are preserved as described earlier. Alternatively, an in-clinic sedimentation technique can be used, in which 0.5 ml of CSF is allowed to sediment over a region of a slide within a sedimentation chamber that is attached to the slide with paraffin or petroleum jelly (Fig. 64-4). The CSF supernate is then gently aspirated with a needle and syringe and can be used for protein or antibody titer determination. Any remaining fluid is then removed by applying blotting paper to the fluid edge, and the slide is quickly dried by vigorously waving it in the air. Once the slide is dry, the remaining paraffin or petroleum jelly should be scraped off. Slides should be evaluated by a veterinary cytopathologist. If the slide cannot reach a commercial laboratory within a few hours, it should be fixed and stained with Diff-Quik Differential Stain Set (American Scientific Products) or Wright's or Giemsa stain.



### FIG 64-4

A sedimentation chamber can be made from a cut section of a glass vacutainer or plastic specimen tube that is attached to a glass microscope slide with paraffin or petroleum jelly. Cerebrospinal fluid (CSF; 0.5 ml) is placed in the chamber. After 30 minutes the supernate is gently aspirated with a needle and syringe and the slide is dried rapidly. The slide is then fixed, and the paraffin or petroleum jelly is removed with a scalpel.

Most of the cells in the CSF of normal dogs and cats are small, well-differentiated lymphocytes (60% to 70%). Minimally vacuolated, large mononuclear phagocytes normally compose up to 40% of the cells. Occasional neutrophils and eosinophils are present, but these cells should not normally make up more than 2% of the cell population. The typical CSF findings in some specific disorders in dogs and cats are summarized in Box 64-3. It is important to realize, however, that CSF cytologic findings must always be interpreted in relation to the signalment, history, and clinical findings.

If blood contamination is severe, it can influence the cytologic findings, but even grossly apparent iatrogenic contamination with peripheral blood will have only a minor impact on WBC count and protein analysis. To approximate the maximum effect blood contamination will have on the WBC count in CSF, one WBC per microliter can be expected for every 500 RBCs per microliter.

The protein concentration in samples collected from the lumbar site (<40 mg protein/dl) is normally higher than the protein content of CSF collected from the cerebellomedullary cistern (<25 mg protein/dl). The protein content of the collected CSF should be determined and, whenever possible, protein electrophoresis performed. An increase in the CSF protein content can occur in diseases that disrupt the bloodbrain barrier, cause local necrosis, interrupt normal CSF flow and absorption, or result in intrathecal globulin production. Information from CSF protein electrophoresis can be used to determine whether the high protein content in CSF is a result of blood-brain barrier disruption, the intrathecal production of immunoglobulin, or both (Box 64-4). CSF protein electrophoresis patterns typical of inflammation, degeneration, and neoplasia of the CNS have been established and can be used with some degree of accuracy to predict the mechanism of disease involved. The immunoglobulins in CSF can also be quantified, helping to differentiate inflammatory from noninflammatory disorders.

Whenever the CSF is cellular, it should be submitted for Gram's staining and anaerobic and aerobic bacterial culture. If infectious disorders are considered likely (see the discussion of meningitis, Chapter 69), specific culture techniques can be applied or, when available, PCR can be used to identify infectious agents in CSF. Antibody titers to a variety of infectious organisms can be measured in CSF, but leakage of antibodies from the serum to the CSF can be problematic. An immunogolobin G (IgG) index greater than 1 indicates that there is significant intrathecal production of immunoglobulin (see Box 64-4). Comparison of CSF and serum titers against a specific organisms can be performed, with a C-value greater than 1 indicating active CNS infection with an organism (see Box 64-4).

### ADVANCED DIAGNOSTIC IMAGING

### **MYELOGRAPHY**

In animals with clinical evidence of spinal cord disease or compression, myelography may be used to confirm, localize,



BOX 64-3

Interpreting Cerebrospinal Fluid Cytology

# Normal: Cell Count <5 White Blood Cells/µl; Protein <25 mg/dl

# Normal cell count and differential; slightly increased protein

Extradural spinal cord compression (disk, tumor, malformation)

Brain neoplasia

Degenerative myelopathy

Fibrocartilagenous embolism

Trauma

**Polyradiculoneuritis** 

### **Lymphocytic Pleocytosis**

Viral meningitis/encephalitis (rabies, distemper)
Necrotizing meningoencephalitis (Pugs, Malteses, York-shire Terriers)

Feline polioencephalomyelitis

Central nervous system lymphoma

# Mixed Cell Pleocytosis (>50 White Blood Cells/ $\mu$ l; Lymphocytes, Mononuclear Phagocytes, Neutrophils, Plasma Cells)

Canine granulomatous meningoencephalitis

Protozoal infection (neosporosis, toxoplasmosis)

Rickettsial infection (ehrlichiosis, Rocky Mountain spotted fever)

Feline infectious peritonitis meningoencephalitis

Lyme neuroborreliosis

Fungal meningoencephalitis (Blastomycosis, Cryptococcosis, Aspergillosis)

### **Neutrophilic Pleocytosis**

Bacterial meningoencephalitis

Fungal meningoencephalitis (Blastomycosis, Cryptococcosis, Aspergillosis)

Steroid responsive meningitis artertis

Rocky Mountain spotted fever

Feline infectious peritonitis meningoencephalitis

Lyme neuroborreliosis

Meningioma

Postmyelographic irritant meningitis

### **Eosinophilic Pleocytosis**

Steroid-responsive eosinophilic meningitis (usually Golden Retrievers)

Parasite migration

Protozoal infection

Fungal meningoencephalitis

Italics signify unusual presentation.

and characterize lesions. This procedure is particularly valuable for identifying compression of the spinal cord by herniated disks or tumors. Myelography is rapid and is more readily available and less expensive than other advanced imaging techniques, such as computed tomography (CT)

and magnetic resonance imaging (MRI), but it is also associated with a higher rate of complications.

To perform myelography, the clinician anesthesizes the animal and injects a nonionic contrast material into the subarachnoid space at the atlanto-occipital or lumbar (L5/6 or L4/5) space. The contrast material most commonly used for this purpose is iohexol (Omnipaque; Nycomed). Injection of iohexal (0.25 to 0.50 ml/kg of 240 or 300 mgl/ml contrast media) is associated with a relatively low (<10%) prevalence of postmyelographic adverse effects, such as seizure, hyperesthesia, and vomiting. Lumbar injections are technically more difficult but associated with decreased risk of iatrogenic spinal cord trauma and improved delineation of thoracic and lumbar compressive spinal cord lesions because the contrast material can be injected under increased pressure and forced around a site of severe compression.

Myelography should be performed only after it has been confirmed that the CSF is not inflammatory because contrast injection will worsen the inflammation and clinical symptoms in an animal with meningitis. Additionally, injection of contrast will cause mild inflammation, making diagnostic evaluation of CSF cytology very difficult for at least 1 week after myelography. CSF collection and analysis should always precede myelography.

In cisternal myelography the needle is inserted using the same technique and landmarks as for cisternal puncture for CSF collection (see Fig 64-1), and the bevel of the needle is directed caudally. The contrast material is injected slowly and allowed to flow caudally the length of the spinal subarachnoid space. Needle removal and elevation of the animal's head, neck, and thorax promote caudal flow, resulting in opacification of the caudal limit of the subarachnoid space within 10 minutes. During myelography the flow of the contrast agent is visualized fluoroscopically (when available), and lateral, ventrodorsal, and sometimes obliquely positioned radiographs are taken directly over each region of interest. In some instances dynamic views (traction, extension, and flexion) may be obtained. If contrast medium filling is inadequate in some regions, the animal is tilted and manipulated to allow gravity-assisted pooling of contrast medium at the site of interest.

Lumbar myelography is performed with the needle at the L5/L6 (large dogs) or L6/L7 (small dogs and cats) site. Needle insertion is as described for lumbar CSF collection, with the bevel of the needle oriented cranially. Once the needle is in place, a small test volume (0.2 ml) of contrast medium should be injected and lateral radiography or fluoroscopy performed to make sure the injection is not directed into the spinal cord parenchyma. If the needle is positioned correctly, the injection is completed during fluorosocopic visualization and then lateral radiographic views are taken with the needle in place. Once the spinal needle is removed, ventrodorsal, oblique, and dynamic radiographs should be taken rapidly because epidural leakage may occur through the puncture site.

Seizures occasionally occur in animals recovering from anesthesia after myelography. Seizures are most common in dogs larger than 29 kg, when cisternal myelography is per-



### Diagnostic Interpretation of Protein and Antibody Concentrations in Cerebrospinal Fluid

Albumin Quotient >0.3 indicates damage to the blood brain barrier and leakage of serum into the CSF.

Albumin Quotient = 
$$\frac{CSF \text{ albumin (mg/dl)}}{Serum \text{ albumin (g/dl)}} \times 10$$

lgG index >1 indicates significant intrathecal antibody production.

$$lgG index = \frac{lgG in CSF}{lgG in serum} \times \frac{1.0}{Albumin Quotient}$$

C-value >1 suggests intrathecal antibody production against a specific organism.

$$\label{eq:continuous} \text{C value} = \frac{\text{organism specific IgG in CSF}}{\text{organism specific IgG in serum}} \times \frac{\text{Total IgG in CSF}}{\text{Total IgG in serum}}$$

Antibody coefficient >1 is the most reliable indicator of intrathecal antibody production against a specific organism (organism A). Organism B is an organism normally expected to have serum antibodies detected.

$$Antibody = \frac{\text{organism A specific IgG in CSF}}{\text{IgG in serum}} \times \text{organism B specific}$$
 
$$Coefficient = \frac{\text{organism A specific IgG in serum}}{\text{IgG in serum}} \times \text{organism B specific}$$

CSF, Cerebrospinal fluid.

formed, and when more than two injections of contrast agent are administered. These seizures can usually be controlled with diazepam (5 to 20 mg, administered intravenously).

Neurologic deterioration occurs in some animals after myelography. Large-breed dogs with cervical spondylomyelopathy (Wobbler syndrome), dogs and cats with inflammatory CNS disease or extradural tumors, and dogs with degenerative myelopathy are most often affected. Fortunately, this deterioration is usually transient.

A normal myelogram will show contrast material filling the subarachnoid space. This appears as a column of contrast agent on each side of the cord on ventrodorsal views and in the ventral and dorsal columns on lateral views (Fig. 64-5). In normal myelograms a slight elevation and thinning of the ventral column of the contrast agent can be seen as it passes over each intervertebral disk space; however, a wide dorsal column remains, indicating that spinal cord compression is not present. Based on the features of the myelogram, a spinal cord lesion can be characterized as extradural compression, intradural extramedullary compression, or intramedullary swelling (Figs. 64-6 and 64-7).

### **ULTRASONOGRAPHY**

Ultrasound is not useful in routine imaging of the brain and spinal cord because these structures are normally encased in bone. This modality can, however, provide valuable information in the diagnostic evaluation of patients with neurologic disease. Abdominal ultrasound is recommended to search for a primary tumor whenever metastatic neoplasia is considered as a possible cause of neurologic signs. Ultrasound can also be used to identify portosystemic shunts in dogs and cats. Brain ultrasound through open fontanelles can be per-

formed to identify hydrocephalus in dogs and cats (Fig. 64-8). Ultrasound of the axilla in a sedated animal can be useful in the identification and biopsy of soft tissue masses within the brachial plexus.

# COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

CT and MRI are available for the diagnosis of neurologic disease at most major veterinary referral centers. These techniques are noninvasive and valuable in the localization, identification, and characterization of many brain and spinal cord lesions (Figs. 64-9 and 64-10). CT is most useful for identification and characterization of bony abnormalities of the vertebral bodies and skull. Contrast-enhanced CT will help identify soft tissue lesions that disrupt vascular endothelium. MRI can be used to determine very small density differences in soft tissues; therefore it is the imaging modality of choice for the brain, spinal cord, and peripheral nerves. These techniques allow precise topographic mapping of lesions, making them valuable tools in the evaluation of compressive lesions of the brain, spinal cord, or cauda equina when surgery is being considered.

### **ELECTRODIAGNOSTIC TESTING**

Electrophysiologic studies can be used to record electrical activity from muscle or neural tissue and aid in lesion localization and characterization. These tests are minimally invasive but usually require sedation or general anesthesia. The cost of the equipment and the experience needed to conduct the studies limit their use to academic and referral clinics.

### **ELECTROMYOGRAPHY**

Normal muscle is electrically silent. As a needle is inserted into normal muscle, a short burst of electrical activity is elicited, which stops when the needle insertion is stopped. Severance, destruction, or demyelination of the peripheral nerve supplying the muscle results in the development of spontaneous fibrillations and positive sharp waves (i.e., denervation potentials) and prolonged insertional activity in affected muscles 5 to 7 days after denervation. These changes may also be seen in some primary muscle disorders. Electromyography (EMG) is most useful to confirm a suspected diagnosis of a muscle or peripheral nerve disorder and to identify abnormal muscles for subsequent biopsy.

### **NERVE CONDUCTION VELOCITIES**

The conduction velocity of motor nerves can be determined by stimulating a nerve at two separate sites and recording the time it takes for an evoked muscle potential to occur. The motor nerve conduction velocity in that segment of nerve can be determined by measuring the distance between the two sites and the difference in the time it takes for the evoked potentials to appear. The conduction velocity of sensory nerves can be measured using a similar technique. Slow conduction times are seen in demyelinating disorders, allowing the diagnosis of peripheral neuropathies. Nerves that have been injured or avulsed and that have degenerated (onset typically 4 to 5 days after injury) do not conduct an impulse; thus nerve conduction velocity testing can also be used to diagnose and localize peripheral nerve injuries.

### **ELECTRORETINOGRAPHY**

An electroretinogram (ERG) is a recording of the electrical response of the retina to a flashing light stimulus. It is an objective way to evaluate retinal function, assessing both rod and cone receptors. The ERG is most useful for the evaluation of blind animals in which the retina appears normal on ophthalmic examination (e.g., diagnosing sudden acquired retinal degeneration) or in which the retina cannot be visualized (e.g., determining whether animals with cataracts have concurrent retinal degeneration). The ERG is abnormal with degenerative disorders of the retina, but it is normal if the

lesion causing visual dysfunction is located caudal to the retina (in the optic nerves, optic chiasm, optic tract, or cerebral cortex). The ERG can be performed under general anesthesia or under sedation if the patient is uncooperative.

# BRAINSTEM AUDITORY EVOKED RESPONSE

The brainstem auditory evoked response (BAER) depicts the response of nervous tissues to an auditory stimulus (a click). The response is a series of waveforms representing activity beginning in the cochlea and being relayed up the auditory pathway in the brainstem. Lesions of the outer, middle, or inner ear; the peripheral vestibulocochlear nerve; and the brainstem caudal to the midbrain cause characteristic changes in the response, aiding in lesion localization. This test has been most widely used for detecting unilateral and bilateral congenital deafness in dogs.

### **ELECTROENCEPHALOGRAPHY**

Electroencephalography provides a graphic record of the spontaneous electrical activity of the cerebral cortex. Results

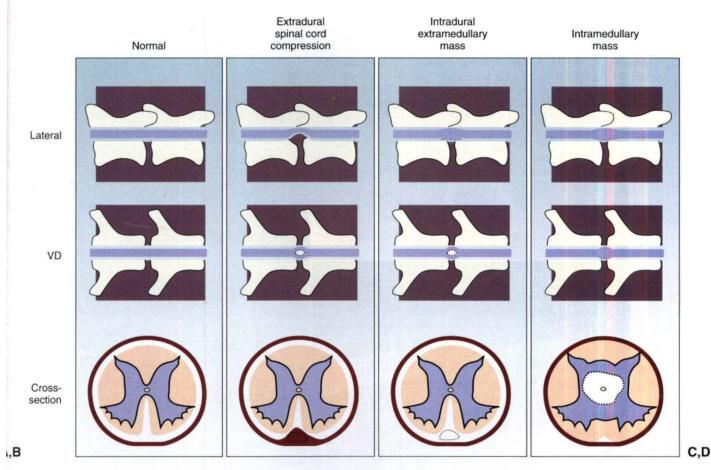




FIG 64-5

Lateral **(A)** and ventrodorsal **(B)** views of a normal myelogram of the thoracolumbar region in a dog. Multiple calcified intervertebral disks can be seen, but no spinal cord compression is evident. (Courtesy Dr. John Pharr, University of Saskatchewan.)

В



### FIG 64-6

The myelographic appearance of extradural, intradural-extramedullary, and intramedullary spinal cord masses. **A,** Normal myelogram. **B,** Ventral extradural spinal cord compression. The leading edge of the contrast material tapers toward the spinal cord, away from the bone on the lateral view. The dorsal column is thinned in this region. On the ventrodorsal view the spinal cord appears widened or flattened, resulting in narrow columns of contrast material. **C,** Ventral intradural, extramedullary spinal cord compression. The leading edge of the contrast material expands and outlines the lesion, tapering toward the spinal cord and toward the bony margin of the osseous canal, resulting in a filling defect at the site of the lesion and the appearance of a "golf tee sign." On the ventrodorsal view the spinal cord appears widened or flattened, resulting in narrow columns of contrast material. **D,** Intramedullary mass or swelling. The leading edges of the contrast material taper toward the bony margin of the osseous canal on both views, with diverging columns of contrast material indicating spinal cord enlargement.

may help determine whether a cerebral disorder is focal or diffuse. Some dogs with epilepsy will have abnormal electroencephalograms (EEGs) between seizures.

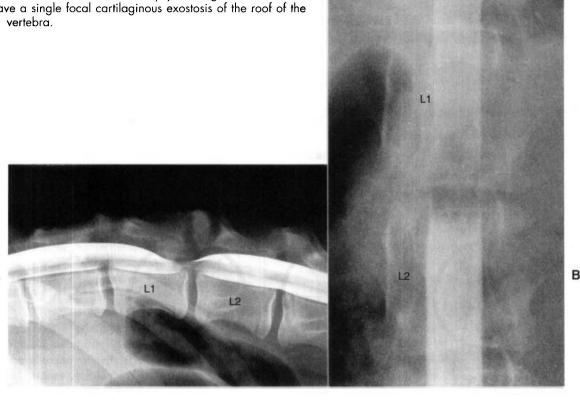
### **BIOPSY OF MUSCLE AND NERVE**

### **MUSCLE BIOPSY**

Muscle biopsy specimens should be evaluated when there is clinical and electrophysiologic evidence of muscular disease. A biopsy may provide a definitive diagnosis or indicate the nature of the disease process. For best results, muscle that is affected should be biopsied and in generalized disorders two different muscles should be sampled. For investigation of myopathic disorders, proximal limb muscles such as the vastus lateralis or triceps should be biopsied, whereas neuropathies are more evident in distal limb muscles such as the cranial tibial or extensor carpi radialis. Because complete histopathologic examination of muscle requires fresh-frozen tissue, most laboratories request that fresh muscle samples be wrapped in a saline-moistened gauze and shippped overnight under refrigeration. Whenever formalin-fixed samples are submitted, the sample should be attached to a splint, such as a tongue depressor, to prevent contraction during fixation.

FIG 64-7

Lateral **(A)** and ventrodorsal **(B)** views of a myelogram in a 5-month-old German Shepherd Dog with a 3-week history of progressive ataxia. A dorsally located extradural compression of the spinal cord within the caudal portion of the L1 vertebra can be seen. At necropsy the dog was found to have a single focal cartilaginous exostosis of the roof of the L1 vertebra.



Routine histologic studies may reveal inflammatory or neoplastic changes and the etiologic agent if the disease is infectious.

When fresh-frozen tissue is evaluated using a full range of enzymatic and immunohistochemical techniques, many characteristics of the muscle can be determined. Based on enzymatic staining characteristics, muscle fibers can be classified according to type and the proportion and distribution of myofiber types described. Some myopathies result in a selective loss of one fiber type. Denervation with reinnervation, as occurs in many neuropathies, results in "type grouping," wherein the normal checkerboard pattern disappears and large clusters of fibers of the same type appear. Muscle fiber shape and size, the presence of degeneration or necrosis, the location of nuclei, the presence of vacuoles or inclusions, and the presence of cellular infiltrates are all evaluated. Immunostains are also available to identify some parasites (Neospora) and evaluate muscles for normal structural components. Muscle samples should be sent to a laboratory with a special interest in muscle disorders to ensure that optimal results are obtained and accurately interpreted. Clinicians should consult the laboratory that will process the biopsy to learn the proper technique of obtaining and preparing specimens and the other procedures to be followed.

### **NERVE BIOPSY**

It may be useful to obtain nerve biopsy specimens in an effort to evaluate peripheral nerve disorders. Nerves are biopsied by transecting approximately one third of the width of the nerve and removing fascicles about 1 cm in length, leaving most of the nerve trunk intact. It is important to biopsy nerves that are affected. The common peroneal nerve and the ulnar nerve are the mixed (i.e., motor and sensory) nerves most commonly biopsied. As with muscle biopsy specimens, nerve biopsy specimens require special handling to ensure that maximal information is obtained. Samples should be laid out on a piece of wooden tongue depressor and pinned at each end to keep them oriented longitudinally, but they should not be stretched. They should then be fixed in 2.5% glutaraldehyde or buffered 10% formalin for light microscopy. Fresh nerve samples can be frozen in liquid nitrogen and stored for biochemical analysis.

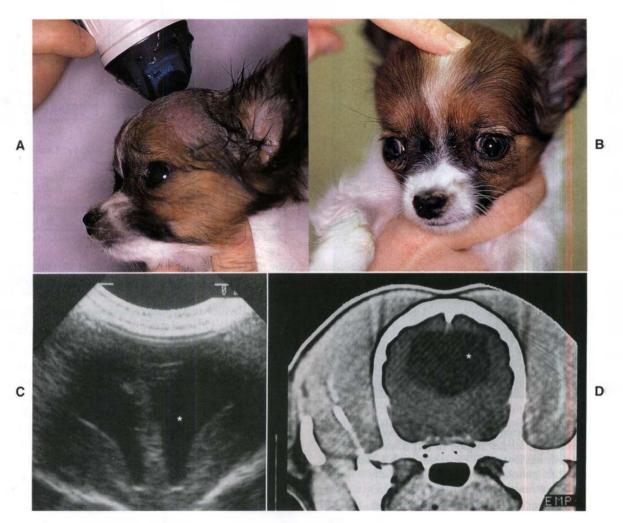


FIG 64-8
Ultrasound image (C) of a young Papillon with hydrocephalus and open fontanelles (A and B). Computed tomography (CT) scan (D) of the head of a dog with hydrocephalus.
\*, Dilated lateral ventricles. (D Courtesy Dr. Greg Daniel, University of Tennessee.)

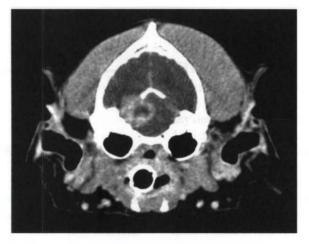


FIG 64-9
Computed tomography (CT) scan of the head of an 11-year-old Golden Retriever with a 5-month history of seizures and a progressive right head tilt. There is a large, cystic, contrast-enhancing mass in the left cerebrum and cerebellum most consistent with a cystic meningioma.

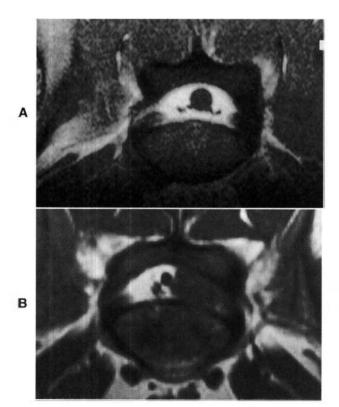
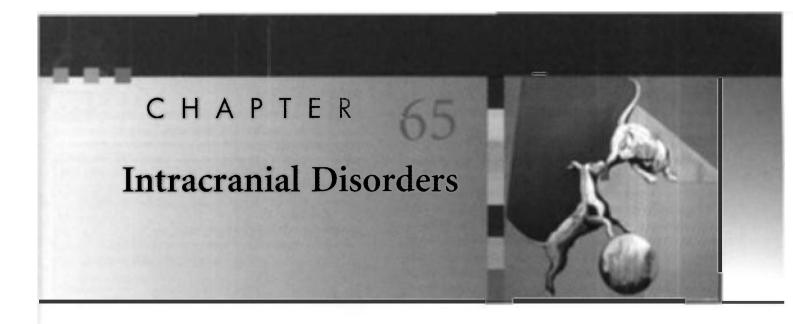


FIG 64-10 Magnetic resonance imaging (MRI) scans (transverse T1 images) of the caudal lumbar region of (A) a normal dog and (B) a Golden Retriever with prolapsed disk material within the vertebral canal. (Courtesy Dr. John Pharr, University of Saskatchewan.)

### Suggested Readings

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### CHAPTER OUTLINE

# GENERAL CONSIDERATIONS ABNORMAL MENTATION

Intoxications

Metabolic Encephalopathies

Diagnostic Approach to Animals with Intracranial Disease

### INTRACRANIAL DISORDERS

Head Trauma

Vascular Accidents

Feline Ischemic Encephalopathy

Hydrocephalus

Lissencephaly

Thiamine Deficiency

Inflammatory Diseases (Encephalitis)

Inherited Degenerative Disorders

Geriatric Canine Cognitive Dysfunction

Neoplasia

### **HYPERMETRIA**

Congenital Malformations

Cerebellar Cortical Degeneration (Abiotrophy)

Neuroaxonal Dystrophy

Brain Cysts

**TREMORS** 

**DYSKINESIAS** 

### **GENERAL CONSIDERATIONS**

When the neurologic examination suggests that a lesion is located above the foramen magnum, a variety of disorders should be considered as differential diagnoses. Some of these disorders typically affect only one particular region of the brain, such as the forebrain or the cerebellum, whereas others can affect any location within the brain. Altered mentation is the first and most pronounced abnormality in most forebrain and brainstem disorders.

### ABNORMAL MENTATION

Abnormal behavior, delirium, compulsive behavior, and seizures can be seen in dogs and cats with lesions of the cerebral cortex and with intoxications or metabolic encephalopathies. Disorders affecting the brainstem can also cause severe depression, stupor, and coma.

When presented with a dog or cat with abnormal mentation, the clinician must first ascertain whether the problem is purely behavioral, the result of systemic illness, or an indication of an intracranial lesion. The history obtained from the owner regarding the animal's normal behavior, systemic signs, and the circumstances preceding the onset of signs may help identify a neurologic problem. Defined neurologic deficits confirm the existence of an abnormality within the nervous system. With some unilateral forebrain lesions animals turn or circle toward the side of the lesion and ignore all sensory input (touch, seeing, and hearing) on the side opposite the lesion (hemi-inattention syndrome). Although their gait will usually be normal, affected animals may exhibit postural reaction deficits on the side opposite the lesion. Brainstem lesions typically cause altered consciousness, multiple cranial nerve deficits, and ipsilateral upper motor neuron (UMN) paresis, ataxia, and postural reaction deficits.

### **INTOXICATIONS**

Intoxication with household toxins, insecticides, rodenticides, and prescription or illicit drugs must be considered in any dog or cat with an acute onset of abnormal mentation. Anxiety and delirium may precede severe depression, seizures, and other neurologic and systemic signs. Common toxic agents causing mentation changes and seizures in dogs and cats include strychnine, metaldehyde, chlorinated hydrocarbons, organophosphates, lead, and ethylene glycol (see Boxes 67-3 and 67-4). The clinical signs of intoxication are usually acute and severe, with rapid deterioration. A history of potential ingestion or exposure to a toxin and the finding of characteristic clinical signs lead to the diagnosis. Treatment must be initiated to remove the toxin, prevent further absorption, and expedite its elimination. Intoxications

resulting in scizures also require emergency treatment for seizures, as described for status epilepticus (see Box 67-7).

### **METABOLIC ENCEPHALOPATHIES**

Animals with abnormal mentation, diminished consciousness, or seizures should always be evaluated for metabolic disturbances such as hepatic encephalopathy, hypoglycemia, severe uremia, electrolyte disturbances, and hyperosmolality (e.g., untreated diabetes mellitus). Depressed mentation can also be a manifestation of severe systemic illness, sepsis, hypoadrenocorticism, or hypothyroid myxedema coma. More detailed information on the diagnosis and management of these metabolic disorders is contained elsewhere in this text.

### DIAGNOSTIC APPROACH TO ANIMALS WITH INTRACRANIAL DISEASE

Intracranial disorders that commonly cause abnormalities of mentation include external trauma, vascular disorders (e.g., hemorrhage and infarction), anomalies (e.g., hydrocephalus, lissencephaly), thiamine deficiency, inflammatory diseases (e.g., encephalitis), degenerative disorders, and primary or metastatic brain tumors. Evaluation should always include a complete physical and neurological examination as well as an ophthalmologic examination. When the cause of the neurologic signs is not readily apparent, animals should be screened for systemic manifestations of inflammatory or neoplastic disease using clinicopathologic tests, thoracic and abdominal radiographs, and abdominal ultrasound. If disease is restricted to an intracranial site, advanced neuroimaging (computed tomography [CT], magnetic resonance imaging [MRI]) and cerebrospinal fluid (CSF) collection and analysis may be required for diagnosis. Degenerative disorders are suspected if all test results are normal (Box 65-1).

### INTRACRANIAL DISORDERS

### HEAD TRAUMA

The outcome for animals with head trauma depends largely on the location and severity of the initial injury. Common causes of head injuries in dogs and cats include motor vehicle accidents and kicks and bites from larger animals. The initial trauma to the brain parenchyma is followed by secondary damage resulting from hemorrhage, ischemia, and edema. Because the brain is enclosed within the bones of the skull, as brain volume increases with edema or hemorrhage, there is an increase in intracranial pressure, leading to decreased cerebral perfusion and further brain damage.

Initial management of a patient with brain injury should focus on recognizing and treating systemic injuries and maintaining adequate circulation and respiration. Systemic hypotension further decreases cerebral perfusion, so fluids should be administered to maintain blood volume (Box 65-2). Administration of synthetic colloids (hetastarch, dextrans) allows rapid restoration of blood volume and pressure without the large volume of fluid required when crystalloids



### Diagnostic Approach to Animals with Abnormal Mentation

- 1. Perform a complete history, physical examination, and neurological assessment.
  - Focal or asymmetrical deficits suggest intracranial disease
- 2. Rule out metabolic encephalopathies. Hematology, serum chemistry profile, urinalysis Blood glucose: fasting, symptomatic, postprandial Liver function test
- 3. Evaluate for systemic inflammatory or neoplastic disease.

Complete ophthalmic examination Thoracic and abdominal radiographs Aspirates of lymph nodes (+/- spleen, liver, bone marrow)

- Serology when appropriate 4. Perform an intracranial examination.
  - Neuroimaging (computed tomography, magnetic resonance imaging)

Cerebrospinal fluid collection and analysis



BOX 65-2

Management of Intracranial Injury

### **Ali Patients**

Establish patent airway, administer oxygen. Examine, assess, and treat concurrent injuries. Treat shock: intravenous fluids, colloids. Maintain mean arterial blood pressure 80-120 mmHg. Monitor neurologic status every 30 minutes.

### If Severe Initial Injury or Deterioration

Elevate head 30 degrees.

Treat seizures if present (see Box 67-6).

Administer 20% mannitol: 1.0 g/kg, administered intravenously over 15 minutes (can repeat in 3 hours).

Administer furosemide: 1.0 mg/kg, administered intravenously.

If intubated, maintain PaCO2 at 30-40 mmHg.

alone are administered. Oxygen should be administered by mask or via nasal or transtracheal catheter. If the animal is unconscious, immediate intubation and ventilation may be required. Hyperventilation reduces intracranial pressure but causes cerebral vasoconstriction and decreased cerebral perfusion; therefore it must be used with caution. Whenever possible, a Paco<sub>2</sub> of 30 to 40 mmHg should be maintained. If seizures are evident, aggressive anticonvulsant therapy should be initiated as for status epilepticus (see Chapter 67) because seizure activity greatly increases intracranial pressure. Measures to lower intracranial pressure include elevating the head at a 30-degree angle from horizontal,



BOX 65-3

### Modified Glasgow Coma Scale

Motor Activity	
Normal gait, normal spinal reflexes Hemiparesis, tetraparesis, or decerebrate activity Recumbent, intermittent extensor rigidity Recumbent, constant extensor rigidity Recumbent, constant extensor rigidity with opisthotonus Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	6 5 4 3 2
Brainstem Reflexes	
Normal pupillary light reflexes and oculocephalic reflexes Slow pupillary light reflexes and normal to reduced oculocephalic reflexes Bilateral unresponsive miosis with normal to reduced oculocephalic reflexes Pinpoint pupils with reduced to absent oculocephalic reflexes Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	6 5 4 3 2
Level of Consciousness	
Occasional periods of alertness and responsive to environment Depression or delirium; capable of responding, but response may be inappropriate Semicomatose, responsive to visual stimuli Semicomatose, responsive to auditory stimuli Semicomatose, responsive only to repeated noxious stimuli Comatose, unresponsive to repeated noxious stimuli	6 5 4 3 2

administration of intravenous mannitol as an osmotic diuretic (1.0 g/kg over 15 minutes), and administration of furosemide (0.7 mg/kg). Administration of high doses of methylprednisolone sodium succinate (SoluMedrol) during the first 6 hours after presentation has been shown to be beneficial in patients with spinal cord injury but may actually be detrimental in patients with serious brain injury.

Systemic and neurological assessment should be repeated every 30 minutes. A scoring system has been developed to allow grading of initial neurological status and serial monitoring. Using the modified Glasgow coma scale (Box 65-3), motor activity, brainstem reflexes, and level of consciousness are all assigned a score from 1 to 6. A total score of 8 or lower is associated with less than 50% survival, even with intensive treatment.

### VASCULAR ACCIDENTS

Spontaneous infarction and hemorrhage occasionally occur in the central nervous systems of dogs and cats. Older dogs;

dogs with renal failure, hyperadrenocorticism, hypothyroidism, or hypertension of any cause; and cats with renal failure, hyperthyroidism, or primary hypertension are predisposed. Intracranial hemorrhage and infarction may also occur secondary to septic emboli, neoplasia, thrombocytopenia, coagulopathies, heartworm disease, or vasculitis. With a vascular accident the onset of neurologic abnormalities is peracute. Results of physical examination, clinicopathologic evaluation, and thoracic radiography may be unremarkable, aside from the neurologic abnormalities, or may reflect the underlying disease process. Systemic blood pressure should be measured and an ocular exam performed to search for hypertension-related hemorrhage or retinal detachment. MRI is the most effective means of making an antemortem diagnosis. CSF analysis, when performed, may reveal increased protein concentration, a mild mononuclear or neutrophilic pleocytosis (<30 cells/µl), and occasionally erythrophagia suggesting prior hemorrhage. Short-term aggressive therapy to lower intracranial pressure as described for head trauma (see Box 64-2) may be indicated. Underlying disorders such as hypertension and coagulopathy should be managed. Most mildly or moderately affected animals show dramatic improvement during the first 3 to 10 days after the onset of signs, although some never return to a normal functional status.

### FELINE ISCHEMIC ENCEPHALOPATHY

Feline ischemic encephalopathy (FIE) is a syndrome of acute cerebral cortical dysfunction caused by cerebral infarction in young and middle-aged cats of any breed and either gender. The portion of the cortex supplied by the middle cerebral artery is most commonly affected. Most cases of FIE are diagnosed during the summer months, and the prevalence of this disorder is highest in cats living in the northeastern United States with access to the outdoors. Cats are presented because of a peracute onset of asymmetric neurologic abnormalities, including delirium, aggression, circling to the side of the lesion, ataxia, and seizures. There may be a loss of proprioception and hyperactive reflexes (UMN signs) in the limbs opposite the side of the lesion, and the cat may be blind but have normal pupillary light reflexes (cortical blindness) on the side opposite the lesion. FIE should be suspected in any cat with an acute onset of nonprogressive unilateral cerebral cortical dysfunction and no history of trauma or evidence of systemic illness or hypertension. Physical examination typically reveals no abnormalities other than the neurologic signs. Ophthalmologic examination, clinicopathologic evaluation, and skull radiography findings are also normal. CSF is normal cytologically, with a normal or only slightly increased protein content, making inflammatory disease unlikely. MRI is the best method of documenting the infarcted region.

Histopathology reveals extensive acute necrosis and edema of the cerebral cortex, resulting from acute infarction of the middle cerebral artery. Moreover, many cats show histopathologic features compatible with aberrant migration of Cuterebra fly larvae. The larvae apparently enter the brain

### **HYDROCEPHALUS**

euthanasia.

Hydrocephalus is a condition in which the cerebral ventricular system is enlarged secondary to an increased amount of CSF, with secondary compression or atrophy of the surrounding neurologic tissue. Most cases are congenital. Dog breeds at risk include the Maltese, Yorkshire Terrier, English Bulldog, Chihuahua, Lhasa Apso, Pomeranian, Toy Poodle, Cairn Terrier, Boston Terrier, Pug, Chow Chow, and Pekingese. Cats are occasionally affected.

sive behavior or recurrent seizures, often resulting in

Many affected animals have an obviously enlarged head and palpably open fontanelles (Fig. 65-1). Care must be taken not to overinterpret these findings, however, because domed heads and open fontanelles are very common in some toy breeds. Although most dogs with fontanelles that remain open at 9 weeks of age do have ventricular dilation, many will never develop clinical signs of hydrocephalus.

Animals with symptomatic hydrocephalus are slow learners and may be difficult to housetrain. They may seem dull or depressed. They may have episodic or constant abnormal behavior, delirium, and cortical blindness. Seizures may occur. Severely affected animals may exhibit tetraparesis and slow postural reactions. Some animals will develop a ventrolateral strabismus (see Fig. 65-1).

Hydrocephalus is suspected on the basis of characteristic signs and physical examination findings in a young animal of a typical breed. If fontanelles are open, ultrasound examination of the brain can be performed through the openings, and this can determine the size of the lateral ventricles and confirm the diagnosis (see Fig. 64-8). If the fontanelles are small or closed, ultrasound scanning is more difficult but may still be attempted through the temporal bone in young animals. Alternatively, CT or MRI can be performed to detect ventricular enlargement. Although historical studies have shown very little correlation between ventricular size and clinical signs, one recent report showed that ventricular enlargement (ventricle: brain [VB] ratio) was correlated







A and B, Hydrocephalus in a Chihuahua puppy. Note the greatly enlarged, domed skull and the divergent strabismus. C, The open skull sutures (fontanelles) are visible in this puppy after surgical drainage of the lateral ventricles with a ventriculoperitoneal shunt.

with severity of clinical signs in small-breed dogs and that all asymptomatic puppies with a VB ratio of >60% went on to develop neurologic signs related to their hydrocephalus.

Long-term medical management of animals with neurologic signs is directed at limiting CSF production and reducing intracranial pressure. Glucocorticoids are administered to decrease CSF production (prednisone, 0.5 mg/kg, administered orally daily, tapered weekly until 0.1 mg/kg q48h). Seizures may be controlled with anticonvulsant therapy, as described for epilepsy (see Chapter 67). The prognosis for a normal life is poor if neurologic signs are present. Surgical drainage and placement of a permanent ventriculoperitoneal shunt have been successful in a few cases.

Acute, severe, and progressive neurologic signs occasionally occur in dogs and cats with hydrocephalus, probably as a result of a sudden increase in intracranial pressure. Therefore it is important to rapidly lower intracranial pressure in these animals, as described for animals with head trauma (see Box 65-2). If fontanelles are open, a ventricular tap can be performed and a small volume of CSF (0.1 to 0.2 ml/kg) can be removed.

### LISSENCEPHALY

Lissencephaly is a rare condition in which the sulci and gyri fail to develop normally, resulting in a smooth cerebral cortex. Cerebellar hypoplasia may be seen in association with this malformation. Lissencephaly has been recognized primarily in the Lhasa Apso, Wire Fox Terrier, and the Irish Setter, Behavioral abnormalities and visual deficits are common. These animals are also very difficult to train and may not be housebroken. If seizures occur, they often are not prominent until the end of the first year of life. Definitive diagnosis requires MRI, brain biopsy, or necropsy.

### THIAMINE DEFICIENCY

Thiamine (vitamin B<sub>1</sub>) deficiency may occur in anorexic cats or cats fed uncooked all-fish diets that contain thiaminase. Thiamine deficiency is almost never seen clinically in dogs, except in racing sled dogs fed a diet high in raw fish. Thiamine deficiency results in abnormal glucose metabolism in the brain, encephalopathy, and hemorrhage of brainstem nuclei. Clinical signs initially include lethargy and ataxia followed by bilateral vestibular ataxia. Ventroflexion of the head and neck, blindness, dementia, head tilt, nystagmus, and seizures may be seen. The tentative diagnosis is based on the dietary history, signalment, and clinical signs and is further supported by the remission of signs within 24 hours of the administration of thiamine (2 to 4 mg/kg/day). Treatment is continued for 5 days or until the deficiency can be corrected.

### INFLAMMATORY DISEASES (ENCEPHALITIS)

Encephalitis resulting from most of the infectious inflammatory disorders discussed in Chapter 69 will result in abnormalities of mentation and seizures. Granulomatous meningoencephalitis (GME), a common noninfectious inflammatory disease in dogs, commonly affects the forebrain, brainstem, or cerebellum to cause a wide range of neurologic abnormalitis. See Chapter 69 for more information regarding the clinical manifestations, diagnosis, and therapy for intracranial inflammatory disorders.

### INHERITED DEGENERATIVE DISORDERS

Metabolic storage diseases are fatal neurodegenerative disorders resulting from an inherited deficiency of enzymes within the cells of the nervous system. Signs develop in young animals and are progressive. Seizures and severe alterations in consciousness may develop. The diagnosis of these disorders is suspected when a young dog of a susceptible breed develops a progressive neurologic disorder with characteristic features. Descriptions of the breed predispositions and clinical features of the inherited degenerative brain disorders can be found in Suggested Readings. Antemortem diagnosis requires brain biopsy or occasionally identification of inclusion bodies in hepatocytes or white blood cells. Histopathologic examination of biopsy specimens from affected organs sometimes reveals characteristic changes, but enzyme assays are required to establish the diagnosis. No treatment is currently available.

### **GERIATRIC CANINE COGNITIVE DYSFUNCTION**

Older dogs with degenerative brain disorders similar to human Alzheimer's disease may develop chronic progressive behavioral abnormalities, including loss of housebreaking, forgetting learned behaviors, altered sleep-wake cycles, and failure to recognize or interact with their owners. Because of the nonspecific clinical signs and the lack of a specific diagnostic test, this syndrome can be diagnosed only after extensive evaluation for other causes of intracranial signs. Older dogs should be carefully evaluated for metabolic disorders, brain tumors, encephalitis, and hypertension-related intracranial dysfunction. If no specific treatable abnormalities are found, administration of antioxidants, omega-3 fatty acids, and selegiline (L-deprenyl: 0.5-1.0 mg/kg/day, administered orally) as well as structured play and environmental enrichment have been recommended. It is difficult to objectively determine the benefit of this treatment.

### **NEOPLASIA**

Brain tumors are common in dogs and cats, usually resulting in a gradual onset of slowly progressive neurologic signs. Clinical signs may also develop acutely if tumors bleed. With the exception of brain lymphoma, most primary and metastatic brain tumors occur in middle-aged and older animals with a median age of 9 years in dogs and 11 years in cats. The most commonly affected breeds include Golden Retrievers, Labrador Retrievers, mixed-breed dogs, Boxers, Collies, Doberman Pinschers, Schnauzers, and Airedale Terriers.

Brain tumors cause signs by destroying adjacent tissue, increasing intracranial pressure, or causing hemorrhage or obstructive hydrocephalus. Seizures are the most common reason for presentation. Circling, ataxia, and head tilt are less

common. As intracranial tumors enlarge, they may cause an increase in intracranial pressure with progressive loss of consciousness and altered mentation; the owner may report that the dog or cat has recently become dull, depressed, and "old." Progressive subtle neurologic signs are sometimes present for weeks or months before the owner notices them.

Some animals with brain tumors are neurologically normal between seizures, but careful neurologic examination usually reveals evidence of asymmetric neurologic dysfunction. Compulsive circling toward the side of the lesion and abnormal postural reactions and vision on the side opposite the lesion are common with forebrain lesions.

Intracranial tumors may be primary (arising from the brain), or they may invade the brain from an adjacent site (e.g., the skull, nose, sinus) or metastasize to the brain from a distant site. A careful physical examination should be performed to identify potential sites of primary neoplasia. Particular attention should be paid to the nose, lymph nodes, spleen, skin, mammary chain, and prostate gland. A complete blood count (CBC), serum biochemistry panel, and urinalysis should be performed to rule out metabolic disease and look for evidence of neoplasia or a paraneoplastic syndrome. Radiography of the thorax and abdomen and abdominal ultrasonography should be performed to search for a primary tumor or extraneural metastases. Many patients with metastatic tumors in the brain have detectable pulmonary metastatic lesions.

Advanced imaging modalities such as CT and MRI are the most valuable imaging techniques for detecting and characterizing intracranial tumors. Although many tumors have characteristic anatomic and imaging features, the tumor type cannot be reliably determined without biopsy.

Because most intracranial tumors are poorly exfoliative, CSF collection and analysis rarely provide a definitive diagnosis. The identification of neoplastic cells in CSF is diagnostic, but this is an unusual finding, except in patients with central nervous system lymphoma, carcinomatosis, and choroid plexus tumors. The classical finding is normal CSF cytology with a slightly increased CSF protein content, but many dogs with brain tumors have completely normal CSF. Some dogs with brain tumors (especially meningiomas) have cellular CSF changes consistent with mixed inflammation, complicating differentiation from disorders such as granulomatous meningoencephalitis.

Treatment for brain tumors depends on the tumor type, tumor location, growth history, and neurologic signs. Once identified with CT or MRI, some small, superficially located, well-encapsulated, benign cerebral tumors; dorsal cerebellar tumors; and bony tumors of the skull are amenable to surgical removal. In particular, there has been some success in the removal of feline cerebral meningiomas. Canine cerebral meningiomas are similarly superficially located and histologically benign, but they are not well encapsulated, making complete surgical removal more difficult. Median survival after surgical removal of primary brain tumors in dogs is approximately 140 to 150 days, with significant risk of mortality within the first 30 days after surgery. For meningiomas,

median survival times are longer (240 days). Surgical removal of feline meningiomas is more successful, with median survival intervals of 22 to 27 months reported.

Traditional radiotherapy is often used as an adjunct to surgery of resectable tumors and as the sole therapy for nonresectable primary (nonmetastatic) brain tumors in dogs. Many dogs that are stable neurologically before therapy show some clinical improvement. Remissions in excess of 1 year are common in dogs with certain brain tumors (e.g., meningioma) treated with radiotherapy alone or with combined surgery and radiotherapy. Boron neutron capture therapy (BNCT) has been used to increase the radiation dose that can be administered to tumor cells while sparing normal brain cells. An important drawback of radiotherapy is that multiple anesthesias and access to a referral center are required.

Supportive chemotherapy can be administered even when definitive therapy is not an option. Corticosteroid administration (prednisone 0.5 to 1.0 mg/kg/day, taper to q48h) may decrease edema surrounding the tumor and improve CSF absorption. Chronic anticonvulsant therapy is administered if necessary. In the event of an acute exacerbation of tumor-related clinical signs, aggressive treatment to lower intracranial pressure is recommended, as outlined for head trauma. Specific chemotherapy for central nervous system lymphoma is possible, but most of the chemotherapeutic agents used for systemic therapy do not cross the blood-brain barrier. Cytosine arabinoside (Cytosar), lomustine (CCNU), and prednisone have some effect (see Chapter 80). Some non-lymphoid brain tumors, especially gliomas, respond to systemic chemotherapy with carmustine (BCNU) or CCNU.

### HYPERMETRIA

A hypermetric gait, with each limb raised excessively during protraction and then returned more forcefully than normal to weight bearing, suggests that there has been a loss of the normal cerebellar regulation of the rate, range, and force of movement. Animals with cerebellar disease are ataxic but strong, with normal postural reactions and spinal reflexes. Affected animals are unable to judge distances or control the range of movements and will make a series of jerking and bobbing movements (intention tremor) when attempting to perform precise movements. A fine tremor of the head and body may also be present at rest. Patients with cervical spinal cord damage to the very superficial spinocerebellar tracts will also exhibit a similar hypermetric gait in all four limbs, but postural reactions (especially knuckling) may be delayed and there will be no head tremor or other brain signs.

Most of the intracranial disorders that cause abnormal mentation or seizures can cause cerebellar dysfunction. Damage to the cerebellum usually occurs through trauma, hemorrhage, infarction, infectious inflammatory disease (see Chapter 69), granulomatous meningoencephalitis (dogs), or primary or metastatic neoplasia. In addition, there are several anomalous and degenerative conditions that specifically

result in cerebellar dysfunction. The diagnostic approach to patients with cerebellar dysfunction is identical to that outlined earlier for patients with abnormal mentation (see Box 65-1).

### CONGENITAL MALFORMATIONS

Malformations of the cerebellum have been described as a congenital anomaly in Chow Chows, Irish Setters, Wire Fox Terriers, and Siberian Huskies and sporadically in many breeds and in cats. Feline cerebellar hypoplasia is most often caused by naturally acquired in utero infection with panleukopenia virus (feline parvovirus) or when a pregnant queen is inoculated with modified-live panleukopenia virus vaccine. Clinical signs of cerebellar hypoplasia become noticeable when the animal first starts to walk, with hypermetria, ataxia, and tremor most apparent. Some cases are mild, and others are very severe, making walking and eating difficult. Because signs do not progress, mildly affected animals can function as pets.

### CEREBELLAR CORTICAL DEGENERATION (ABIOTROPHY)

Cerebellar abiotrophy is a syndrome of premature degeneration of cells within the cerebellum. Cells develop normally but later degenerate because of an intrinsic cellular defect. Rarely, the degeneration occurs in neonates, with signs evident at first ambulation and progressively worsening over weeks to months. In most breeds clinical signs begin between 3 and 12 months of age, but adult onset cerebellar abiotrophies (Brittany, Gordon Setter, Old English Sheepdog, American Staffordshire Terrier, and Scottish Terrier) occasionally are apparent between 2 years and 8 years of age. In addition to the abiotrophies, metabolic storage diseases occasionally cause progressively worsening cerebellar signs in juvenile or young adult dogs and cats. Diagnosis of all of these conditions is based on cerebellar biopsy or necropsy. No treatment is effective.

### **NEUROAXONAL DYSTROPHY**

Neuroaxonal dystrophy is a slowly progressive degenerative disorder affecting nerve cell bodies within gray matter throughout much of the central nervous system, with most severe lesions within the spinocerebellar tracts and the Purkinje cells. Young adult Rottweilers (1 to 2 years old) are initially presented for a hypermetric gait and ataxia, and signs progress slowly over 2 to 4 years. Affected dogs develop an intention tremor, a constant fine tremor, nystagmus, and menace deficits. Postural reactions (knuckling and hopping) remain normal. A similar disorder has been documented in young (2- to 4-month-old) Collies, Chihuahuas, Boxers, German Shepherd Dogs, and tricolor kittens (5 to 6 weeks old). Diagnosis requires biopsy or postmortem, and there is no effective treatment.

### **BRAIN CYSTS**

Epidermoid, dermoid, and arachnoid cysts occasionally compress the cerebellum, causing progressive neurologic signs, including hypermetria. The cysts can be identified on CT or MRI imaging and surgically drained or removed.

### **TREMORS**

A tremor is a rhythmic, oscillatory movement of a body part. Intention tremors of the head, usually associated with cerebellar disease, substantially worsen as the animal intends to initiate movement, as when the head nears a target during goal-oriented movement such as attempts to eat, drink, or sniff an object. Action tremors occur throughout movement and disappear with rest.

A toxic cause should be suspected in an animal with severe generalized tremors or tetany (increased muscle tone or rigidity) of acute onset (see Box 67-3). Strychnine, metaldehyde, chlorinated hydrocarbons, mycotoxins, and organophosphates are the most common toxic causes of tremors and tetany. Drug-induced tremor can be associated with metaclopramide, fentanyl/droperidol, or diphenhydramine administration. Metabolic disturbances such as hypoglycemia and hypocalcemia will also cause tremors, muscle fasciculations, and tetany.

Generalized head and body tremors unassociated with a metabolic or toxic disorder may arise acutely in young adult (5 months to 3 years of age) small-breed dogs. Historically, this disorder was first identified only in white dogs (Maltese, West Highland White Terrier), and the syndrome was called "little white shaker syndrome"; however, it is now known that dogs of any color can be affected. A fine tremor develops rapidly over 1 to 3 days. The tremor worsens with excitement and decreases during sleep. Neurologic findings are usually normal, although hypermetria, nystagmus, head tilt, or seizures have been observed in a few dogs. All clinicopathologic test results are normal. Occasionally, CSF analysis reveals a mild lymphocytosis and slightly increased protein content. Histological examination reveals a mild, nonsuppurative meningoencephalomyelitis with perivascular cuffing. In some dogs the tremors decrease and subside 1 to 3 months after onset, even without treatment, but they persist for life in other dogs. Diazepam (0.5 mg/kg, administered orally q8h) and corticosteroids (prednisone, 2 to 4 mg/kg/day, administered orally) administered early in the disease usually result in clinical improvement within 4 or 5 days. Treatment should be tapered gradually over 4 or 5 months, and drug doses titrated to control clinical signs. Relapse months to years later may require retreatment or lifelong low-dose therapy in a few dogs.

Tremor syndromes have also been reported in young dogs and cats with metabolic storage diseases or congenital spongy degeneration of the central nervous system. A congenital diffuse tremor syndrome associated with abnormal development of myelin in the central nervous system has been observed in puppies. Affected puppies stand with a widebased stance and show whole-body tremors that worsen with exercise or excitement. This syndrome is progressive and severe in male Welsh Springer Spaniels, usually resulting in death within 2 to 4 months. Less severe tremor syndromes have been recognized in the Weimaraner, Bernese Mountain Dog, Samoyed, Dalmatian, and Chow Chow as well as sporadically in other breeds, with signs apparent by 4 weeks of age. Diagnosis is based on the signalment and clinical findings in the absence of other neurologic deficits or clinicopathologic abnormalities. In the Chow Chow and in other mildly affected breeds, gradual clinical recovery may occur within 1 to 3 months without treatment.

Trembling of the pelvic limbs (senile tremors) may develop in old dogs that are weak but otherwise neurologically normal. The trembling disappears at rest but is apparent when the animals stand, and it worsens with exercise. Results of all tests are normal, and there is no effective treatment. Diagnostically, it is important to rule out electrolyte disturbances, hypothyroidism, hypoadrenocorticism, hip dysplasia, and lumbosacral disease.

### **DYSKINESIAS**

Dyskinesias are central nervous system disorders that result in involuntary movements in fully conscious individuals. These movement disorders have only occasionally been described in dogs and cats and may be difficult to distinguish from focal seizures or stereotypical behavior disorders. The abnormal electrical activity initiating these movements originates in the subcortical extrapyramidal basal nuclei of the multisynaptic corticospinal tract. The resulting extrapyramidal signs consist primarily of episodic, unpredictable, rhythmic, involuntary limb hyperextension or hyperflexion; head

bobbing; or the adoption of abnormal postures. Movement disorders thought to be dyskinesias have been reported in Norwich Terriers, Cavalier King Charles Spaniels, Malteses, and Soft Coated Wheaten Terriers. A syndrome of intermittent head-bobbing occasionally recognized in Boxers, English Bulldogs, and Doberman Pinschers may also be a dyskinesia.

### Suggested Readings

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# CHAPTER Loss of Vision and Pupillary Abnormalities

### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
NEUROOPHTHALMOLOGICAL EVALUATION

Vision

Menace Response

Pupillary Light Reflex

Dazzle Reflex

Pupil Size and Symmetry

Disorders of Eyeball Position and Movement

Lacrimal Gland Function

LOSS OF VISION

Lesions of the Retina, Optic Disk, and Optic Nerve

Lesions of the Optic Chiasm

Lesions Caudal to the Optic Chiasm

HORNER'S SYNDROME

PROTRUSION OF THE THIRD EYELID

### **GENERAL CONSIDERATIONS**

Loss of vision or pupillary abnormalities may be detected during the physical examination of an animal examined because of neurologic dysfunction or may be the primary reason for presentation. Owners rarely recognize a visual deficit until it is bilateral and complete, at which time the animal is brought in because of an apparently sudden onset of blindness. When an animal is evaluated because of loss of vision, it is important first to determine whether or not the animal is actually blind and to perform a complete ocular and neuroophthalmological examination.

# NEUROOPHTHALMOLOGICAL EVALUATION

### VISION

Vision should initially be assessed by observing the animal's response to the environment, including its ability to negotiate doorways and stairs and the attention it pays to rolling

or falling silent objects such as cotton balls. If unilateral vision loss is suspected, the normal eye should be covered during testing. For vision to be present the entire visual pathway must be intact. This includes the retina; the optic nerve, which passes through the optic chiasm to the optic tract to synapse in the lateral geniculate nucleus (LGN) in the diencephalon; and axons projecting to the visual cortex in a band of fibers called the *optic radiation*. Most of the optic nerve axons cross in the optic chiasm (particularly those carrying information from the lateral visual field) and are continued in the contralateral optic tract, LGN, and optic radiations to the visual cortex (Fig. 66-1). The visual cortex must be functional for the animal to process and respond appropriately to visual cues.

### **MENACE RESPONSE**

The menace response is a cortically mediated blink produced by a threatening gesture (Fig. 66-2). The sensory part of this response involves each of the components of the visual pathway (see Fig. 66-1). Normally, the visual stimulus is directed at the nasal retina (i.e., the menacing gesture is in the lateral visual field coming from the side), and because almost all of the optic nerve axons that originate in the nasal retina cross in the optic chiasm, primarily the contralateral visual cortex is assessed. The information interpreted in the visual cortex is forwarded to the motor cortex to initiate a blink response, requiring a functional facial nerve (CN7). The menace response is also coordinated in the cerebellum, with unilateral cerebellar lesions causing ipsilateral loss of the menace response but no loss of vision. The absence of a menace response could therefore be a result of ocular, retinal, or optic nerve disease; damage to the contralateral forebrain; an altered mental state; cerebellar disease; or an inability to blink (CN7 deficit; Box 66-1). This learned response may not be present in puppies and kittens younger than 12 weeks of age.

### **PUPILLARY LIGHT REFLEX**

The pupillary light reflex (PLR) should always be assessed, whether or not an animal is able to see. A bright light is directed into the pupil, and the pupil is assessed for

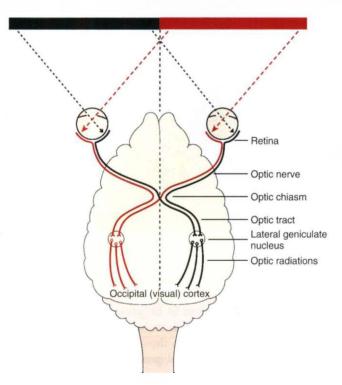


FIG 66-1 The visual pathways.



FIG 66-2

The menace response is performed by making a threatening movement toward each eye in turn. The expected response is a blink. The stimulus is primarily directed toward the nasal retina, assessing the contralateral visual cortex.

constriction (direct reflex). The opposite pupil should simultaneously constrict (consensual response). The sensory visual pathway is the same as that described for the menace response except that some optic tract axons synapse before the LGN in the pretectal nucleus located at the junction between the midbrain and the thalamus. Most of the axons arising from this nucleus cross midline again and synapse in the parasympathetic component of the oculomotor nucleus ipsilateral to the eye being stimulated. Stimulation of the parasympathetic axons of the oculomotor nerve (CN3)



BOX 66-

Lesions Causing Loss of the Menace Response in Dogs

### Loss Of Menace

Severe ocular disease Retinal disease Visual pathway lesion Ipsilateral optic nerve

Optic chiasm

Contralateral optic tract, lateral geniculate nucleus, optic radiation

Contralateral visual cortex (forebrain) lesion

Altered mental status

Metabolic encephalopathy

Severe systemic illness

Cerebellar disease

Inability to blink (CN7)

Immature reflex (<12 weeks of age)

results in pupil constriction. Because some of the axons leaving the pretectal nucleus do not cross, there is also stimulation of the contralateral oculomotor nucleus, resulting in a somewhat weaker consensual pupillary response. The pupillary response to light can be minimal if the light used is not bright enough, if the animal is nervous and has high resting sympathetic tone, or if there is ocular disease (iris atrophy or greatly increased intraocular pressure) preventing pupillary constriction. The pupillary light response requires fewer functional photoreceptors and optic nerve axons than vision, so partial lesions of the proximal visual pathways (retina, optic nerve, optic chiasm, optic tract) can sometimes cause loss of vision with normal PLRs, similar to lesions of the forebrain (Table 66-1).

### **DAZZLE REFLEX**

The dazzle response is the generation of a rapid blink when a very bright light is directed into the eye. The sensory visual pathway is as described for the PLR in that this is a subcortical ipsilateral reflex that does not require the visual cortex, but the motor pathway is mediated by the facial nerve (CN7) rather than the oculomotor nerve. A negative dazzle response in a blind eye suggests retinal or optic nerve disease. A positive dazzle response in a blind eye supports central (brain) disease.

### PUPIL SIZE AND SYMMETRY

Pupil size and symmetry should be assessed in room light as well as in darkness to evaluate the ability of the pupils to constrict (parasympathetic function) and to dilate (sympathetic function). Pupil abnormalities causing dilation (mydriasis) or constriction (miosis) of only one pupil will result in anisocoria. If the abnormal pupil is unable to constrict, the anisocoria caused by mydriasis in the affected



**TABLE 66-1** 

Localization of Visual Pathway Lesions Based on Vision and Pupillary Light Reflexes

LOCATION OF COMPLETE LESION	VISION IN RIGHT EYE	VISION IN LEFT EYE	LIGHT IN RIGHT EYE	LIGHT IN LEFT EYE
Right retina/eye* Bilateral retina/eye* Right optic nerve Bilateral optic nerves Optic chiasm (bilateral) Lesion caudal to optic chiasm (right lateral geniculate nucleus, right optic radiation, or right visual cortex)	Absent Absent Absent Absent Absent Normal	Normal Absent Normal Absent Absent	No response either eye No response either eye No response either eye No response either eye No response either eye Both pupils constrict	Both pupils constrict No response either eye Both pupils constrict No response either eye No response either eye Both pupils constrict
Bilateral lesion caudal to optic chiasm Right oculomotor nerve	Absent Normal	Absent Normal	Both pupils constrict Left pupil constricts; right pupil is dilated, no response	Both pupils constrict Left pupil constricts; right pupil dilated, no response

Retinal or eye lesions must be very severe to cause loss of pupillary light reflexes.

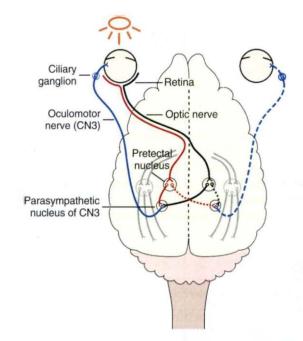


FIG 66-3
The pathway of the pupillary light reflex.

eye will be most apparent in bright light. Anisocoria caused by a single miotic pupil, such as is seen in animals with Horner's syndrome, will be most apparent in a darkened room as the normal pupil dilates. A complete ophthalmic examination should be performed to ascertain whether pupillary abnormalities can be explained by nonneurologic abnormalities of the eye. Iris atrophy, iris hypoplasia, and glaucoma will cause mydriasis, whereas uveitis and painful conditions of the cornea commonly cause miosis. Hippus, a condition in which there are exaggerated oscillations of

pupillary size in response to light, can be an indication of central nervous system disease.

# DISORDERS OF EYEBALL POSITION AND MOVEMENT

During the neurologic examination it is important to evaluate eye position and movement. The extraocular muscles are innervated by the oculomotor nerve (CN3), the trochlear nerve (CN4), and the abducent nerve (CN6), with lesions resulting in an abnormal eye position (strabismus) or failure of the eye to move appropriately when the head is moved during evaluation of the vestibulo-ocular reflex (see Chapter 63). Strabismus can occur with lesions of individual nerves, but most often paralysis of all of the extraocular muscles (external ophthalmoplegia) occurs with a mass in the region of the paired cavernous sinuses on the floor of the calvarium adjacent to the pituitary gland (cavernous sinus syndrome). Mass lesions in this area typically also damage the parasympathetic pupillary fibers in the oculomotor nerve (CN3), causing a fixed midrange or mydriatic pupil with normal vision (internal ophthalmoplegia). Ipsilateral damage to the ophthalmic and maxillary branches of the trigeminal nerve result in diminished corneal and medial palpebral sensation and occasionally atrophy of the ipsilateral masticatory muscles.

### LACRIMAL GLAND FUNCTION

The lacrimal gland and the lateral nasal gland are innervated by the parasympathetic portion of the facial nerve. Normal function is assessed by performing a Schirmer tear test and examining the ipsilateral nostril for dryness. Facial nerve lesions result in a loss of the palpebral reflex because of an inability to blink, decreased basal tear production, and a dry nose. Sensory innervation of the cornea is provided by the trigeminal nerve (CN5), and corneal stimulation by touch, cold, wind, or other irritants normally results in a blink

response and increased reflex tear production. Lesions of the ophthalmic branch of the trigeminal nerve (CN5) result in decreased reflex tear production and decreased blink frequency, which may lead to keratitis and corneal ulceration.

### LOSS OF VISION

# LESIONS OF THE RETINA, OPTIC DISK, AND OPTIC NERVE

Concurrent loss of vision and diminished or absent PLR indicate the presence of a lesion affecting both the visual and PLR pathways. Unilateral severe lesions of the retina, optic disk, or optic nerve before the optic chiasm result in impaired vision and loss of the direct PLR in the affected eye as well as a loss of the PLR in the opposite eye (the consensual response) when light is directed in the affected eye (see Table 66-1). The direct and consensual response to light directed in the unaffected eye should be normal. Ocular or optic nerve disease must be very severe to cause complete loss of PLRs. Whenever an animal is evaluated for blindness, the retina should be carefully examined to rule out disorders such as progressive retinal atrophy, retinal dysplasia, retinal detachment, retinal hemorrhage, and chorioretinitis. Optic nerve atrophy secondary to glaucoma or trauma must also be eliminated as a cause of blindness and PLR loss.

### **Sudden Acquired Retinal Degeneration**

Sudden acquired retinal degeneration syndrome (SARDS) is an idiopathic syndrome causing sudden bilateral degeneration of retinal photoreceptors in dogs. Middle-aged and old dogs of any breed can be affected, with females and obese individuals predisposed. The primary presenting complaint is loss of vision, with complete blindness occurring over a

period of hours to weeks and often overnight. Pupils are dilated and PLRs are sluggish in dogs examined shortly after vision loss and absent in dogs with advanced disease. Many affected dogs have concurrent polyuria, polydipsia, panting, weight gain, and lethargy. Clinical, serum biochemical, and urinalysis findings may be typical of hyperadrenocorticism, but endocrine tests and advanced imaging of the pituitary and adrenal glands rarely confirm that disorder. In the early stages of SARDS both fundi appear normal, but with time the retinal changes become indistinguishable from chronic retinal degeneration caused by other conditions. SARDS is differentiated from retrobulbar optic neuritis by its extinguished (flat-line) electroretinogram (ERG). The pathogenesis of the disorder appears to be localized production of antibodies directed against retinal neurons. No consistent response to treatment has been reported, but the administration of intravenous immunoglobulin infusions may be of some benefit early in the course of SARDS. Systemic signs are usually transient and resolve without treatment, but the blindness is permanent.

### Optic Neuritis

Inflammation of the optic nerves causes blindness and loss of PLRs (Fig. 66-4). Fundoscopic evaluation may reveal optic disk swelling and discoloration (red) with or without associated retinal detachment and hemorrhage. When optic neuritis occurs posterior to the globes (i.e., retrobulbar), the visible portion of the optic nerves will be normal. In dogs with blindness and loss of PLRs with a normal fundus, ERG is required to differentiate bilateral retrobulbar optic neuritis (normal ERG) from SARDS (flat-line ERG).

Optic neuritis is most commonly seen as an isolated idiopathic immune-mediated disorder affecting one or both optic nerves, but it may also be a manifestation of systemic

Neurologic exa		• ERG (evaluate retina)	
History Physical examination		Ophthalmologic examination • Examine PLR	

Retina	Optic nerve	Optic chiasm	Caudal to chiasm
Chorioretinitis Retinal detachment Retinal degeneration • Progressive retinal atrophy (PRA) • Central progressive retinal atrophy (CPRA) • Sudden acquired retinal degeneration (SARD)	Optic neuritis Congenital optic nerve hypoplasia Infectious inflammatory disease GME	Infectious inflammatory disease     Neoplasia     Infarct     GME	Hydrocephalus     Lissencephaly     Lysosomal storage disease     Metabolic encephalopathy     Lead poisoning     Cerebral infarct     Infectious inflammatory disease     GME     Neoplasia

FIG 66-4

Diagnostic approach to a dog or cat with loss of vision.



BOX 66-2

### Disorders Associated with Optic Neuritis

### Infectious Disease

Canine distemper Ehrlichiosis Toxoplasmosis

Feline infectious peritonitis

Cryptococcosis

Blastomycosis

Systemic aspergillosis

Bacterial disease

Feline leukemia virus

### **Inflammatory Disease**

Granulomatous meningoencephalitis Systemic lupus erythematosus Steroid responsive meningitis arteritis

### **Neoplastic Disease**

Systemic neoplasia Intracranial neoplasia

Idiopathic Immune-Mediated Optic Neuritis

disease (Box 66-2), especially canine distemper, ehrlichiosis, mycotic disease, and granulomatous meningoencephalitis (GME). Diagnosis of idiopathic (immune-mediated) optic neuritis is made only after infectious and neoplastic disorders are ruled out during a thorough workup for systemic and intracranial disease, including a complete blood count (CBC), serum chemistry profile, urinalysis, heartworm antigen test, serologic screening for infectious diseases, thoracic radiography, and cerebrospinal fluid (CSF) collection and analysis. Magnetic resonance imaging (MRI) can be used to eliminate mass lesions of the optic chiasm. If all test results are normal, primary immune-mediated optic neuritis is tentatively diagnosed.

Treatment of idiopathic optic neuritis should be initiated with orally administered corticosteroids (prednisone 1 to 2 mg/kg/day). If a favorable response is seen (i.e., improved vision and PLRs), then the dose of steroids should be gradually decreased over 2 to 3 weeks until alternate-day therapy is achieved. If there is no initial response to steroid therapy, then the prognosis for return of vision is poor. Untreated optic neuritis leads to irreversible optic nerve atrophy and permanent blindness. Even with appropriate therapy, many cases will progress or relapse.

### **Papilledema**

Edema of the optic disk usually indicates that there is increased intracranial pressure caused by a cerebral tumor or inflammatory mass lesion. This is seen as an enlarged optic disk with indistinct or fluffy margins and kinking of blood vessels as they pass over the disk. Papilledema may be difficult to distinguish on fundoscopic evaluation from



FIG 66-5
Neoplasm of the optic chiasm identified with magnetic resonance imaging in a 7-year-old Doberman Pinscher with an acute onset of bilateral blindness, loss of pupillary light reflexes, and no other neurologic deficits.

optic neuritis, although patients with a significant forebrain lesion causing papilledema should have clinical evidence of forebrain disease, including abnormal mentation, behavior change, and seizures. Despite reports that papilledema does not affect vision, most patients with papilledema caused by increased intracranial pressure are cortically blind.

### LESIONS OF THE OPTIC CHIASM

Lesions of the optic chiasm result in a failure of transmission of the visual image and the light stimulus, causing blindness, normal fundic examination, normal ERG, bilateral mydriasis, and loss of the direct and consensual PLRs in both eyes. Neoplasia and other space-occupying masses can occur at this location, especially lymphoma (cats), pituitary macroadenomas, meningiomas, and primary nasal tumors extending into the brain (Fig. 66-5; see also Fig. 66-4). Vascular lesions such as hemorrhage and infarction, infectious inflammatory granulomas, and granulomatous meningoencephalitis can also affect the optic chiasm. Evaluation should include a search for evidence of extraneural infectious or neoplastic disease followed by MRI, CSF collection and analysis, and endocrinologic testing as warranted.

# LESIONS CAUDAL TO THE OPTIC CHIASM

Lesions in the lateral geniculate nucleus, optic radiations, or visual cortex prevent interpretation of the image, resulting in a normal fundic examination, normal ERG, normal PLRs (direct and consensual), and blindness in the eye opposite the side of the lesion. With unilateral lesions of the optic tracts or optic radiations the visual deficits are most com-

plete in the lateral visual field of the contralateral eye and the medial visual field of the ipsilateral eye. Other clinical signs of forebrain disease, such as seizures, circling, and decreased consciousness, are expected with forebrain lesions severe enough to cause visual deficits. Causes of intracranial blindness (i.e., central or cortical blindness) include traumainduced hemorrhage and edema, vascular infarcts, GME, infectious encephalitis, central nervous system neoplasia, congenital disorders (e.g., hydrocephalus, lissencephaly), and degenerative disorders (lysosomal storage diseases). Animals with functional disturbances of the forebrain caused by metabolic encephalopathies, lead intoxication, hypoxia, or postictal depression may also present with cortical blindness. Diagnostic evaluation for intracranial blindness should follow guidelines outlined in Chapter 65 and should include thorough physical, ophthalmologic, and neurologic examinations; a laboratory database; screening thoracic and abdominal radiographs; CSF analysis; and CT or MRI evaluation.

### HORNER'S SYNDROME

Lesions affecting the sympathetic innervation to the eye result in Horner's syndrome. This condition causes miosis (constriction of the affected pupil), drooping of the upper eyelid (ptosis), and an inward sinking of the eyeball (enophthalmos). The third eyelid (nictitating membrane) is often partially protruded (Box 66-3; Fig. 66-6).

Horner's syndrome can result from injury to the sympathetic innervation to the eye anywhere along its pathway (Box 66-4; Fig. 66-7). Lesions are classified as first order (central), second order (preganglionic), or third order (postganglionic) according to the level of the lesion along the sympathetic pathway.

First order neurons originate in the hypothalamus and rostral midbrain and travel down the tectotegmental spinal tract, coursing through the brainstem and cervical spinal cord to terminate at the preganglionic cell bodies in the thoracic spinal cord. Upper motor neuron lesions in the brainstem or cervical spinal cord are a relatively rare cause of Horner's syndrome but may occur secondary to trauma, infarction, neoplasia, or inflammatory disease. Ipsilateral hemiplegia and other concurrent neurologic abnormalities are expected in these animals (see Box 66-4).

The preganglionic cell bodies of the second order neurons are located in the lateral horn of the spinal cord gray matter at the level of the first three thoracic spinal cord segments (T1-T3). The second order axons leave the spinal cord with



BOX 66-3

### Components of Horner's Syndrome

Miosis Enophthalmos **Ptosis** Prolapsed nictitans the T1 to T3 ventral nerve roots. The sympathetic axons then leave the spinal nerves to form the thoracic sympathetic trunk, which courses cranially within the thorax. The axons continue to course cranially within the vagosympathetic trunk in the cervical region and synapse in the cranial cervical ganglion, ventral and medial to the tympanic bulla at the base of the skull. Injury to second order neurons can occur when there is damage to the spinal cord at the cervical intumescence (C6-T2) caused by trauma, infarcts, neoplasia, or



Horner's syndrome in a domestic short-haired cat with otitis media/interna.



### Common Causes of Horner's Syndrome

### First Order (Central) Causes (Rare)

Intracranial neoplasia, trauma, infarct Cervical spinal cord lesion Intervertebral disk protrusion Neoplasm Fibrocartilaginous embolism Trauma

### Second Order (Preganglionic) Causes

Spinal cord lesion T1-T3 (trauma, neoplasia, fibrocartilaginous embolism)

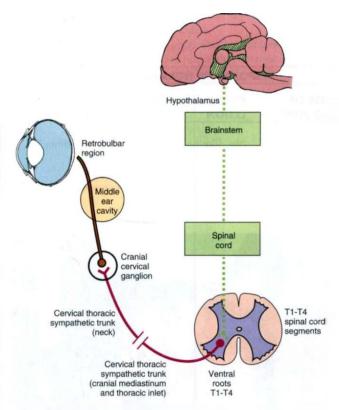
Brachial plexus avulsion Thoracic spinal nerve root tumor Cranial mediastinal mass Cervical soft-tissue neoplasia, trauma Skull base trauma

### Third Order (Postganglionic) Causes

Otitis media/interna Neoplasia in middle ear Retrobulbar injury, neoplasia

### **Unknown Causes**

Idiopathic



**FIG 66-7**Sympathetic innervation to the eye. An injury anywhere along this pathway will result in Horner's syndrome.

inflammatory disease. Affected animals will exhibit lower motor neuron signs in the affected forelimb, upper motor neuron signs in the ipsilateral rear limb, and Horner's syndrome. In animals with brachial plexus avulsion there will be complete lower motor neuron paralysis of the affected limb and an ipsilateral Horner's syndrome that may be partial (miosis only) because of sparing of the T3 (and sometimes T2) nerve roots (Fig. 66-8). Horner's syndrome can also occur when the second order neurons are damaged by thoracic surgery, mediastinal masses (lymphoma or thymoma), bite wounds to the neck, strangulation injuries, invasive thyroid carcinoma, or errors made during thyroid-ectomy or surgery for cervical intervertebral disk disease. Physical and neurologic findings are often useful in localizing preganglionic Horner's syndrome.

Most dogs and cats with Horner's syndrome have post-ganglionic lesions. The postganglionic (third order) axons for ocular sympathetic innervation course rostrally through the tympanooccipital fissure into the middle ear and enter the cranial cavity with the glossopharyngeal nerve (CN9), leaving the cranial cavity via the orbital fissure for distribution to the smooth muscle of the orbit, the upper and lower eyelids, the third eyelid, and the iris muscles. Third order Horner's syndrome is common in patients with otitis media or neoplasia within the middle ear, often accompanied by evidence of peripheral vestibular (CN8) disturbance and sometimes facial nerve (CN7) paralysis. Rarely, retrobulbar

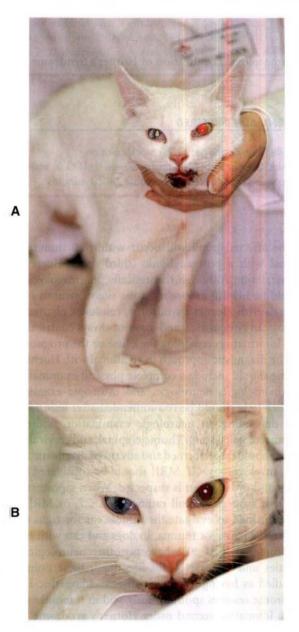


FIG 66-8
Horner's syndrome (A) in a domestic short-haired cat with traumatic right brachial plexus avulsion (B).

injury, neoplasia, or abscessation will result in a third order Horner's syndrome.

Pharmacologic testing has been recommended to help localize the cause of Horner's syndrome in dogs and cats (Table 66-2). This testing can be used to help determine the most likely site of the lesion. When the Horner's syndrome has been present for at least 2 weeks, denervation hypersensitivity will occur secondary to the loss of sympathetic innervation. A single drop of a very dilute concentration of a direct-acting sympathomimetic (0.1% phenylephrine: stock 10% solution diluted 1:100 with saline solution) is applied to both eyes, using the unaffected eye as a control. Because this dilute solution does not normally induce pupillary dilation, the pupil in the normal eye should not dilate. Dilation



### Pharmacologic Localization of Horner's Syndrome

	RI	ESPONSE OF NORMAL PUPIL		
AGENT ADMINISTERED	RESPONSE OF AFFECTED PUPIL	PREGANGLIONIC LESION	POSTGANGLIONIC LESION	
O.1% Phenylephrine: (10% stock solution Neo-Synephrine, Winthrop; diluted 1:100 in saline) Apply 2 drops topically; evaluate at 20 minutes	No dilation	No dilation	Dilation within 20 minutes	

of the affected pupil will occur within 20 minutes in an animal with a postganglionic (third order Horner's syndrome) lesion. Although, theoretically, pharmacologic testing should be helpful in localizing the site of neuron injury in animals with Horner's syndrome, results of pharmacologic testing can be equivocal and may not always contribute practical information regarding the cause or the prognosis.

The diagnostic approach in an animal with Horner's syndrome should include a complete physical examination and ophthalmologic, neurologic, and otoscopic examinations. Further tests should be recommended after lesion localization depending on neurologic examination findings and pharmacologic testing. Thoracic, spinal, and cervical radiography should be performed and advanced diagnostic imaging (e.g., myelography, CT, MRI) should be considered if a first or second order lesion is suspected. When a postganglionic lesion is suspected, skull radiographs, CT, or MRI should be performed to evaluate the middle ear for signs of otitis media, neoplasia, or trauma. In dogs and cats with Horner's syndrome, at least 50% have no other neurologic abnormalities and a cause is not identified; these animals are classified as having idiopathic disease. Idiopathic Horner's syndrome resolves spontaneously within 6 months in most dogs. Idiopathic second order Horner's syndrome is especially common in Golden Retrievers.

### PROTRUSION OF THE THIRD EYELID

In dogs and cats the third eyelid may protrude over the corneal surface in the presence of corneal or conjunctival irritation or space-occupying retroorbital disease. This may also occur if the animal experiences a decrease in periorbital mass as a result of dehydration, a loss of retrobulbar fat or muscle (Fig. 66-9), or a loss of volume within the eye (i.e., microphthalmos, phthisis bulbi).

Protrusion of the third eyelid is a conspicuous feature of Horner's syndrome (with miosis) and also of dysautonomia (with mydriasis). Systemic illness or tranquilization can also result in third eyelid protrusion in some dogs and cats. A peculiar syndrome (e.g., Haw's syndrome) has been observed in cats, and occasionally in dogs, in which a dramatic bilateral third eyelid protrusion of no obvious cause is observed.



### FIG 66-9

Dramatic muscle atrophy in a dog with masticatory muscle myositis has resulted in retraction of the globes into the orbits and protrusion of the third eyelid over most of the corneal surface.

Affected cats are usually younger than 2 years of age and in good health otherwise, although digestive disturbances or heavy intestinal parasite loads have occasionally been documented. The instillation of sympathomimetic drops (phenylephrine 10%) causes the membrane to rapidly retract. The condition resolves spontaneously within several weeks or months.

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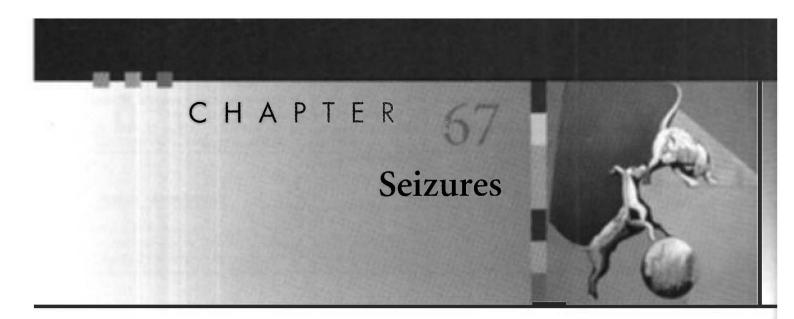
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### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
SEIZURE DESCRIPTIONS
SEIZURE CLASSIFICATION AND LOCALIZATION
DIFFERENTIAL DIAGNOSIS

Idiopathic Epilepsy
Intracranial Disease
Probable Symptomatic Epilepsy
Extracranial Disease
DIAGNOSTIC EVALUATION

ANTICONVULSANT THERAPY ANTICONVULSANT DRUGS

Phenobarbital Potassium Bromide

Diazepam

Clorazepate

Felbamate

Gabapentin

Zonisamide

Levitiracetam

ALTERNATIVE THERAPIES

EMERGENCY THERAPY FOR DOGS AND CATS IN STATUS EPILEPTICUS

### **GENERAL CONSIDERATIONS**

A seizure is the clinical manifestation of excessive or hypersynchronous abnormal electrical activity in the cerebral cortex. The clinical features of seizures can be separated into four components: the prodrome, aura, ictal period, and postictal period. The prodrome is the period of time before the seizure begins, when the owner may report unusual behavior such as hiding, attention seeking, whining, or agitation. The prodrome may be barely noticeable in some animals and distinct enough to enable owners to accurately predict seizure onset in others. The aura is the initial manifestation of the seizure, when animals exhibit stereotypical sensory or motor activity (pacing, licking, swallowing), autonomic patterns (salivation, vomiting, urination) or abnormal behavior (barking, attention seeking) for seconds to minutes before seizure onset. The ictal period is the seizure itself, when the animal exhibits a variety of signs that may include loss or derangement of consciousness, altered muscle tone, jaw chomping, salivation, and involuntary urination and defecation. This phase usually lasts only seconds to minutes. The postictal period immediately follows the seizure and can last from a few seconds to several hours, during which time the animal may exhibit abnormal behavior, disorientation, altered thirst or appetite, somnolence, or blindness as well as defined sensory and motor neurological deficits. Epilepsy is a chronic neurologic condition characterized by recurrent seizures.

Dogs and cats are occasionally affected by nonepileptic paroxysmal disorders, during which they may experience altered behavior, collapse, abnormal movements, transient neurologic symptoms, or paralysis. Distinguishing these disorders from seizures is important for diagnosis and treatment. Cardiac arrhythmias causing syncope; weakness caused by hypoglycemia, hypocortisolemia, or electrolyte disturbances; acute vestibular "attacks"; narcoleptic or cataplexic events; and weakness caused by myasthenia gravis are all examples of such paroxysmal events. Descriptions of the event and the animal's activity and demeanor immediately preceding and following the event will help distinguish these events from seizures (Box 67-1). One helpful distinguishing feature is that only seizures should have an associated postictal period.

### SEIZURE DESCRIPTIONS

Most seizures in dogs and cats are tonic-clonic, generalized motor seizures in which the animal experiences a period of extremely increased extensor muscle tone (tonus), falls into lateral recumbency, and then has periods of tonus alternating with periods of relaxation (clonus), resulting in rhythmic



BOX 67-1

### Paroxysmal Disorders Confused with Epileptic Seizures

Syncope (reduced cerebral bloodflow) cardiac arrhythmias hypotension Episodic weakness hypoglycemia low blood cortisol electrolyte disturbances Myasthenia gravis Acute vestibular "attacks" Movement disorders Episodic falling Scotty cramp

Head bobbing Dyskinesias

Sleep disorders Narcolepsy

Cataplexy

Obsessive compulsive disorder

BOX 67-2

### Common Disorders Resulting in Seizures

### Extracranial Causes

Toxins

Metabolic diseases

Hypoglycemia

Liver disease

Hypocalcemia

Hyperlipoproteinemia

Hyperviscosity

Electrolyte disturbances

Hyperosmolality

Severe uremia

### Intracranial Lesions: Symptomatic Epilepsy

Congenital malformations Hydrocephalus

Lissencephaly

Neoplasia

Primary brain tumors

Metastatic tumors

Inflammatory disease

Infectious inflammatory disease

Granulomatous meningoencephalitis

Necrotizing encephalitis

Vascular disease

Hemorrhage

Infarct

Metabolic storage diseases

Degenerative conditions

Scar Tissue: Probable Symptomatic Epilepsy

Idiopathic Epilepsy (Primary Epileptic Seizures)

contractions of muscles manifested as paddling or jerking of the limbs and chewing movements. Animals are usually unconscious during these seizures, although their eyes may remain open.

Less common than generalized, symmetric tonic-clonic seizures in dogs and cats are focal partial motor seizures. These seizures arise in part of one cerebral hemisphere, resulting in asymmetric signs that may include turning of the head away from the side of the lesion and focal twitching or tonic-clonic contractions of the contralateral facial or limb muscles. Some focal seizures are primarily manifested as altered consciousness and bizarre behaviors (psychomotor seizures), which may include aggression, howling, "fly biting," pacing, circling, restlessness, and staggering. It can sometimes be very difficult to distinguish psychomotor seizures from compulsive stereotypic behavior. Focal seizures may progress to generalized motor seizures in some animals. Although it is often stated that partial motor seizures are usually associated with structural brain disease, many dogs with idiopathic epilepsy experience focal seizures with secondary generalization.

### SEIZURE CLASSIFICATION AND LOCALIZATION

Seizure disorders are classified according to their cause as being idiopathic, intracranial, or extracranial in origin (Box 67-2). Idiopathic epilepsy is diagnosed in approximately 25% to 30% of dogs having seizures but is uncommon in cats. Animals with idiopathic epilepsy have no identifiable extracranial or intracranial cause for their seizures and no concurrent neurologic abnormalities, and their seizures are presumed to be genetically based. Approximately 35% of dogs with seizures and most cats with seizures have an identifiable structural intracranial lesion (e.g., anomaly, inflammation, neoplasia, trauma) that is causing seizures, and these animals are said to have symptomatic epilepsy. A very small number of patients have seizures believed to be secondary to a scar or residual brain damage following a previous insult, but this structural lesion is difficult to demonstrate; such animals are classified as having probable symptomatic epilepsy. Extracranial causes such as the ingestion of toxins or metabolic or endocrine derangements also result in seizures.

Seizure activity always indicates a functional or structural abnormality of the forebrain, particularly of the frontal or temporal lobes of the cerebrum. Metabolic and toxic disorders cause seizures through functional alterations of the balance between inhibitory and excitatory neurotransmitters. Defined, localizing neurologic deficits are unlikely to be detected interictally (between seizures) in patients with extracranial causes of seizures. Animals with an intracranial lesion causing symptomatic epilepsy may exhibit myriad signs leading to forebrain neurolocalization, including behavior change, circling toward the side of the lesion, contralateral hemiparesis and postural reaction deficits, and



BOX 67-3

Intoxications Resulting in Acute Neurologic Dysfunction

### Strychnine

Common use: rat, mole, gopher, and coyote poison Clinical findings: stiff extension of legs and body, erect ears, tetanic spasms induced by auditory stimuli

Diagnosis: history of access or ingestion, characteristic signs, chemical analysis of stomach contents

Treatment: vomiting (if no neurologic signs), gastric lavage, diazepam as needed, pentobarbital to effect; establish diuresis

### Metaldehyde

Common use: snail, slug, and rat poison

Clinical findings: anxiety, hyperesthesia, tachycardia, hypersalivation, muscle fasciculations, and tremors; not worsened by auditory stimuli; nystagmus in cats; may convulse; depression, respiratory failure

Diagnosis: history of access or ingestion, characteristic signs, acetaldehyde odor on breath, analysis of stomach contents

Treatment: gastric lavage, pentobarbital to effect, endotracheal tube and ventilation if necessary; establish diuresis

### Chlorinated Hydrocarbons

Common use: agricultural products and insecticides; lipidsoluble products are usually absorbed through skin

Clinical findings: apprehension, hypersensitivity, hypersalivation, exaggerated response to stimuli, muscle twitching of face and neck progressing to severe fasciculations and tremors; tonic-clonic seizures may occur

Diagnosis: history of access, characteristic signs, insecticide smell to haircoat, analysis of stomach contents

Treatment: wash with warm soapy water to prevent further exposure; if ingested (rare), gastric lavage and instill activated charcoal; pentobarbital to effect

### Organophosphates and Carbamates

Common use: insecticides

Clinical findings: excessive salivation, lacrimation, diarrhea, vomiting, and miosis; twitching of facial and tongue muscles, progressing to extreme depression and tonic-clonic seizures

Diagnosis: history of exposure, characteristic signs, analysis of stomach contents, low serum acetylcholinesterase activity

### Organophosphates and Carbamates—cont'd

Treatment: prevent further exposure; wash if topical exposure; gastric lavage and activated charcoal if ingested; atropine (0.2 mg/kg IV initially and 0.2 mg/kg SC as needed q6-8h); pralidoxime (20 mg/kg IM q12h) if within 48 hours of exposure or if was dermal exposure

### Lead

Common use: ubiquitous in environment in linoleum, rug padding, old lead-based paints (before 1950s), putty and caulking material, roofing materials, batteries, grease, used motor oil, golf balls, fishing sinkers, pellets, and lead shot

Clinical findings: gastrointestinal signs of anorexia, abdominal pain, vomiting and diarrhea, and megaesophagus; neurologic signs of hysteria, aggression, nervousness, barking, tremors, seizures, blindness, hypermetria and nystagmus (cats), and dementia

Diagnosis: history of exposure, characteristic signs, CBC changes (basophilic stippling of RBCs, increase in nucleated RBCs); blood lead level (heparinized tube: >0.5 ppm [50 mg/dl], diagnostic; >0.25 ppm, suggestive); radiographs may reveal radiopaque material in gastrointestinal system

Treatment: emetics, gastric lavage, activated charcoal, enemas; surgery or endoscopy if lead in stomach; specific: calcium ethylenediaminetetraacetic acid (Ca EDTA) to chelate lead and hasten excretion (25 mg/kg IV q6h as 10 mg Ca EDTA/ml in dextrose for 2-5 days); establish diuresis; alternative treatment: succimer (10 mg/kg PO for 10-14 days; Chemet; Sandofi Pharm, N.Y.)

### Ethylene Glycol

Common use: automobile antifreeze, color film processing solutions

Clinical findings: ataxia, severe depression, polyuria-polydipsia, vomiting; seizures are rare

Diagnosis: history of exposure, characteristic signs, severe metabolic acidosis, calcium oxalate crystalluria; eventually, decreased urine production and acute renal failure; diagnosis and treatment of this disorder are discussed in detail in Chapter 44

contralateral vision loss and facial hypalgesia. Some animals with small lesions will, however, be normal interictally, with no other defined neurologic deficits.

Idiopathic epilepsy is a condition wherein the seizure threshold is decreased. This can be caused by intrinsic neurotransmitter imbalances, genetic mutations affecting ion channels, or other functional abnormalities. Epileptic foci contain cells with an intrinsic pattern of high spontaneous firing, leading to seizure activity. Idiopathic epilepsy has been shown to be inherited in a few dog breeds, and a familial basis for the condition is suspected in others. Affected

animals are normal interictally, and extensive diagnostic evaluation, including histologic examination of the brain, is normal.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a patient with seizures includes idiopathic epilepsy, intracranial disease (symptomatic epilepsy), probable symptomatic epilepsy, and extracranial disease.

### **IDIOPATHIC EPILEPSY**

Idiopathic epilepsy is the most common cause of seizures in the dog and is characterized by repeated episodes of seizures with no demonstrable cause. Affected dogs are normal between seizures. Idiopathic epilepsy is uncommon in cats; most cats with seizures have an identifiable intracranial cause, such as neoplasia or encephalitis.

Idiopathic epilepsy is inherited in German Shepherd Dogs, Belgian Tervurens, Keeshonds, Beagles, and Dachshunds. On the basis of pedigree analysis, genetic factors are also strongly suspected in Labrador Retrievers, Golden Retrievers, and Collies. Epilepsy is also commonly seen in Saint Bernards, Cocker Spaniels, Irish Setters, Boxers, Siberian Huskies, English Springer Spaniels, Alaskan Malamutes, Border Collies, Shetland Sheepdogs, Miniature Poodles, and Wire Fox Terriers. It is seen sporadically in almost all breeds, mixed-breed dogs, and cats.

The initial onset of seizures usually occurs between 6 months and 3 years of age, although seizures are not observed until 5 years of age in some dogs. In most breeds it seems that the younger the age at the onset of a seizure disorder, the more difficult the disorder will be to control. A difficultto-control seizure disorder develops at a very young age in some purebred dogs (e.g., 8- to 12-week-old Cocker Spaniels), but such animals may then outgrow the problem by 4 to 6 months of age. This form of epilepsy is termed juvenile epilepsy.

The seizures in dogs and cats with idiopathic epilepsy are usually generalized, tonic-clonic, and associated with a loss of consciousness lasting from 1 to 2 minutes. Some dogs, especially Labrador Retrievers and Miniature Poodles, may instead experience a mild, generalized type of seizure in which they remain alert but anxious while they exhibit a crouched stance, uncontrollable trembling, muscular rigidity, or disequilibrium. Many of these dogs experience a postictal phase and develop more classical generalized tonic-clonic seizures later in life, confirming that these events are seizures. A similar syndrome identified in Chinooks (a Northern breed) may be a paroxysmal movement disorder (dyskinesia) rather than a seizure disorder.

Simple or complex focal seizures with or without secondary generalization may also occur in animals with idiopathic epilepsy. Seizures typically recur at regular intervals, with weeks or months intervening between the seizures. As the animal ages, the frequency and severity of seizures may increase, especially in large-breed dogs. In some dogs, particularly those of large breeds, seizures can eventually occur in clusters, in which multiple seizures occur during a 24hour period. Clusters of seizures are not usually seen in association with the first seizure in dogs with idiopathic epilepsy, except in Border Collies, Dalmatians, and German Shepherd Dogs. If more than two seizures occur during the first week of a seizure disorder, a progressive intracranial or extracranial cause should be suspected.

Idiopathic epilepsy is the most likely diagnosis in a young adult, neurologically normal animal with a long history (>1 year) of a nonprogressive intermittent seizure disorder and a lengthy interictal period (>4 weeks). Findings from a complete physical, neurologic, and ophthalmologic evaluation and results of routine clinicopathologic tests are normal. Intracranial evaluation, when performed, is normal (Fig. 67-1).

### INTRACRANIAL DISEASE

Symptomatic epilepsy is a direct result of intracranial disease localized in the forebrain. Congenital and infectious inflammatory conditions are most often seen in young animals, whereas neoplasia is the most common cause in dogs and cats older than 6 years of age. Most of the intracranial disorders discussed in Chapter 65 and the inflammatory disorders discussed in Chapter 69 can cause symptomatic epilepsy (see Box 67-2). Focal or multifocal neurological deficits identified interictally may suggest structural forebrain pathology, but not all patients with symptomatic epilepsy will have an abnormal neurologic examination. Diagnosis requires careful physical, neurological, and ophthalmologic examination; evaluation for concurrent systemic manifestations of infectious and neoplastic disorders; and often intracranial evaluation, including cerebrospinal fluid (CSF) analysis, and advanced diagnostic imaging (computed tomography [CT] or magnetic resonance imaging [MRI]).

### PROBABLE SYMPTOMATIC EPILEPSY

Scar tissue-related acquired epilepsy can occur after an inflammatory, traumatic, toxic, metabolic, or vascular insult. If a history of significant trauma or infection can be ascertained, the event usually precedes the onset of the seizure disorder by 6 months to 3 years. Findings from physical and neurologic examinations, clinicopathologic tests, and CSF analysis are normal. It is not usually possible to detect a structural abnormality using MRI, and even necropsy will not reliably demonstrate a lesion. The treatment is the same as for idiopathic epilepsy (i.e., anticonvulsant therapy), but the prognosis for seizure control in some large-breed dogs may be better for those with scar tissue-related acquired epilepsy than for those with idiopathic epilepsy.

### **EXTRACRANIAL DISEASE**

Hypoglycemia, hepatic encephalopathy, hypocalcemia, and primary hyperlipoproteinemia may cause seizures in dogs and cats. Other metabolic alterations, including hyperviscosity syndromes (e.g., multiple myeloma, polycythemia), severe electrolyte disturbances (e.g., hypernatremia), hyperosmolality (e.g., untreated diabetes mellitus), heatstroke, and prolonged severe uremia, also occasionally cause seizures (see Box 67-2). In many of these disorders intermittent nonneurologic clinical signs and physical examination findings point toward an extracranial cause of the seizures. Most metabolic encephalopathies also intermittently or permanently alter consciousness, manifesting as confusion, delirium, or depression at least intermittently. Results of a complete blood count (CBC), serum biochemistry panel, and urinalysis often help establish the diagnosis. Hepatic encephalopathy resulting from portosystemic shunting can

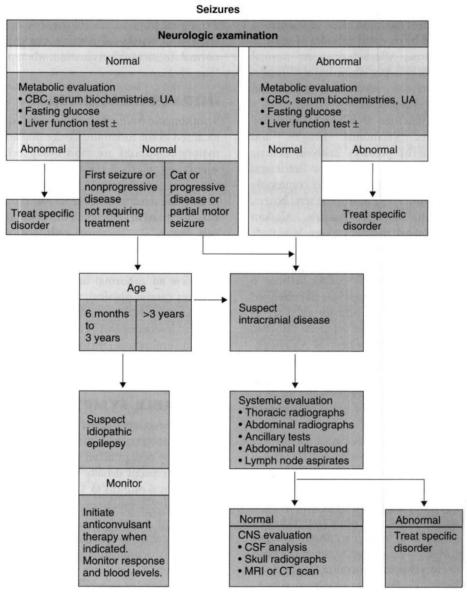


FIG 67-1
Diagnostic approach used in dogs or cats with seizures.

occasionally cause seizures in the absence of other clinical or clinicopathologic abnormalities, especially in cats, so evaluation of liver function is an important component of the initial evaluation for metabolic causes of seizures. More detailed information on the diagnosis and management of these metabolic disorders is contained elsewhere in this text. Common intoxications causing seizures are described in Box 67-3, and treatment of intoxications is outlined in Box 67-4.

### DIAGNOSTIC EVALUATION

A complete and accurate history must be obtained in every animal presenting for a seizure. The owner's description is critical to determine whether the observed paroxysmal event

was actually a seizure and to characterize any seizures as generalized, focal, or psychomotor. The relationship of seizures to daily activity (e.g., exercise, sleep, eating, excitement), seizure duration, and a description of any observed postictal abnormalities should be recorded. Owners should be asked whether they have noticed any changes in the animal's behavior, gait, vision, or sleep patterns in the weeks or months preceding the seizure, characteristics that might indicate a structural forebrain lesion. Recent systemic signs such as cough, vomiting, diarrhea, polyuria, polydipsia, and weight loss or weight gain should also be recorded. Vaccination status, diet, potential exposure to infectious causes of encephalitis, access to drugs or toxins, and history of serious head injury should also be determined. When seizures have occurred intermittently over a prolonged period of time (weeks to months), the seizure pattern and frequency should



BOX 67-4

### **Emergency Treatment of Intoxications**

### **Prevent Further Absorption of Intoxicant** Remove intoxicant from skin and haircoat

1. Toxin was cutaneously absorbed.

How: 1. Remove flea collar if that is source of toxin.

- 2. Wash animal in warm, soapy water; rinse and repeat.
- 3. Flush with warm water for 10 minutes.

### Induce emesis

If:

- 1. Ingestion of intoxicant occurred less than 3 hours before presentation.
- Product ingested was not a petroleum distillate, strong acid, or strong base.
- 3. Animal has a normal gag reflex and is not convulsing or very depressed (danger of aspiration).

- How: 1. At home can recommend syrup of ipecac, 6.6 ml/ kg. Use this in cats.
  - 2. Administer apomorphine subcutaneously (0.08 mg/kg) or in conjunctival sac (1 crushed tablet or 1 disk [6 mg]: rinse eye with saline solution after emesis).
  - 3. Administer xylazine (cats, 0.44 mg/kg IM).

Save vomitus for analysis.

### Gastric lavage

- 1. Ingestion of intoxicant occurred less than 3 hours before presentation.
- 2. Attempts to produce emesis were unsuccessful or emesis was not recommended.

- How: 1. Induce anesthesia and place cuffed endotracheal tube.
  - 2. Lower head relative to body.
  - 3. Pass a large-bore stomach tube to level of stomach.

### Prevent Further Absorption of Intoxicant-cont'd Gastric lavage-cont'd

- 4. Use water (5-10 ml/kg body weight) for each washing; aspirate with syringe.
- 5. Repeat 10 times.

Save stomach contents for analysis.

### Gastrointestinal adsorbents

- How: 1. If gastric lavage has been performed, administer activated charcoal slurry (10 ml/kg of 1 g of activated charcoal/5 ml of water) as last lavage. Let this sit for 20 minutes, then administer a cathartic.
  - 2. If gastric lavage was not performed, administer slurry (dose as above) via stomach tube or administer tablets of activated charcoal.

### Cathartics

How: 1. Sodium sulfate 40% solution should be administered (1 g/kg PO) 30 minutes after activated charcoal is administered.

### Diuresis

How: 1. Administer saline solution to effect diuresis.

2. Mannitol (20% solution, 1-2 g/kg IV) or furosemide (2-4 mg/kg IV) may be added to enhance diuresis if needed.

### Administer Specific Antidotes

See Table 69-3.

**Supportive and Symptomatic Care** 



BOX 67-5

### Indications for Initiating Chronic Anticonvulsant Therapy

- 1. Unresolvable intracranial disease causing seizures
- 2. Cluster seizures
- 3. At least one episode of status epilepticus
- 4. Interictal period less than 12 to 16 weeks
- 5. Increasing seizure frequency or severity

be assessed and the owner should be asked to record frequency and severity of all future seizures on a calendar to allow objective evaluation of disease progression or response to therapy. When idiopathic epilepsy is considered likely, owners should be encouraged to contact the breeder to ascertain whether litter mates or other related dogs are affected.

Physical, ophthalmologic, and neurologic examinations should be obtained in every animal presented for seizures. In the immediate postictal period transient symmetric neurologic abnormalities such as blindness, altered consciousness, and postural reaction deficits are common, so these should not be overinterpreted. Neurologic abnormalities that persist beyond the postictal period suggest an intracranial cause for seizures requiring further evaluation. Lymph node and abdominal palpation as well as mammary gland and prostate examination should be performed to evaluate for primary neoplasia that could have spread to the brain. Some animals with toxic or metabolic causes of seizures will also have specific abnormal findings on physical examination, which aid in diagnosis. Results of these examinations will be normal in dogs and cats with idiopathic epilepsy as well as in many patients with intracranial and extracranial causes of seizures.

Every animal evaluated for seizures should undergo routine screening laboratory tests, including a CBC, serum biochemistry panel, and urinalysis. Blood glucose should also be measured during observed neurologic signs or after a 12-hour fast. Liver function should be evaluated in dogs

and cats that are less than 1 year of age at the time of their first seizure and in all animals with initial laboratory results suggesting hepatic dysfunction (see Chapter 36).

The animal's signalment and history as well as the onset and progression of the seizure disorder allow ranking of likely differential diagnoses. Congenital structural disorders such as hydrocephalus and lissencephaly are the most likely causes of a seizure disorder in a very young animal. Infectious causes of encephalitis usually cause rapidly progressive neurologic dysfunction rather than seizures alone. In aging animals cerebral neoplasia, vascular accidents, and acquired metabolic disturbances are more likely causes of seizures. Animals with idiopathic epilepsy typically have their first observed seizure between 6 months and 3 years of age; thus it is not a likely diagnosis in a dog or cat with seizures that began late in life.

When the systemic, neurologic, and screening laboratory tests are all normal, recommendations for further testing are based on history and signalment. Dogs between 1 and 3 years of age when their first seizure is observed, presenting with a single generalized seizure or a history of a few generalized seizures weeks or months apart, most likely have idiopathic epilepsy; further evaluation may not be required. Typically, the frequency and severity of the seizures are monitored, and, when necessary, treatment is initiated with anticonvulsant therapy. Idiopathic epilepsy is uncommon in cats; therefore, even when all routine screening tests are normal, cats should be tested for feline leukemia virus and antibody against feline immunodeficiency virus, and intracranial evaluation should be recommended.

Further testing, including intracranial evaluation, should be recommended in all dogs with interictal neurologic abnormalities, in dogs older than 5 years of age when their first seizure is observed, and in dogs with focal seizures or multiple seizures that take place within a 1-month period. When neurologic or systemic signs are present that could be caused by infections diseases endemic to the region, noninvasive and relatively inexpensive serologic testing may be beneficial. Thoracic and abdominal radiographs and abdominal ultrasound should be performed to look for systemic manifestations of infectious causes of symptomatic epilepsy and for primary or metastatic neoplasia. If these tests are negative, advanced imaging of the brain with MRI or CT is performed, as well as CSF collection and analysis.

### ANTICONVULSANT THERAPY

Management of dogs and cats with seizures can be attempted using anticonvulsant therapy. Because this requires a large financial, emotional, and time commitment by owners, they should be involved in the decision to initiate treatment. Not every animal with seizures requires anticonvulsant therapy, but there is compelling evidence that dogs treated early in the course of their seizure disorder may have better long-term control of their seizures compared with dogs that are allowed to have many seizures before treatment is initiated.



### Guidelines for Anticonvulsant Therapy in Dogs

- 1. Initiate treatment with PB (2.0 mg/kg PO q12h).
- If the seizures continue to occur after 48 hours of treatment, double the dose.
- At least 10 days after initiating therapy, measure the trough (prepill) serum PB concentration. If the concentration is less than 25 μg/ml (107 μmol/L), increase the PB dose by 25% and reevaluate the serum concentration 2 weeks later. Repeat until the trough serum PB concentration is between 25 and 35 μg/ml (107 to 150 μmol/L).
- If seizures are adequately controlled, maintain dose and monitor serum PB concentration and liver enzymes/ function once twice a year.
- 5. If there is inadequate seizure control despite adequate trough serum PB concentration, measure serum PB peak (4 hours postpill) and trough (prepill) concentrations. If there is more than a 25% variation, increase PB administration to three times a day.
- If seizure control is still inadequate, add potassium bromide therapy (15 mg/kg PO q12h with food).
- 7. If necessary to control seizures, increase the dose of potassium bromide to 20 mg/kg PO q12h.
- Measure the trough potassium bromide concentration in 3 to 4 months. It should be 1.0 to 2.0 mg/ml (10-20 mmol/L).

PB, Phenobarbital; PO, by mouth.

Anticonvulsant therapy should be initiated in all dogs and cats with the following: (1) seizures caused by an intracranial lesion, (2) one or more episodes of cluster seizures or status epilepticus, (3) seizures that occur more often than once every 12 to 16 weeks, or (4) seizures that are becoming more frequent (Box 67-5).

Complete control of seizures in dogs and cats with idiopathic epilepsy is rarely possible, but a decrease in the frequency and severity of seizures is a realistic goal that can be accomplished in 70% to 80% of animals. Owners should keep a log detailing the frequency and severity of seizures so that the effects of the medication can be monitored. Adverse effects of the medication and plans for monitoring blood concentrations and dose adjustments should be discussed. Emergency situations, such as status epilepticus, should be described to owners and specific recommendations for treatment and veterinary assistance provided. A minimum database, including a CBC, serum biochemistry profile, and urinalysis, should always be obtained immediately before the start of anticonvulsant therapy, and if one was not recently performed, a liver function test is also recommended. Whenever possible, animals should be initially treated with a single anticonvulsant drug (monotherapy) to decrease the prevalence of adverse effects, optimize owner compliance, and decrease overall costs of drugs and monitoring. Clinical response and therapeutic drug concentrations should be monitored to determine the proper dose of anticonvulsant drug for the individual animal. If the initial drug administered is ineffective in spite of optimal serum drug concentrations, then another antiepileptic drug should be added or substituted (Box 67-6).

### ANTICONVULSANT DRUGS

### **PHENOBARBITAL**

Phenobarbital (PB) has been considered the drug of choice for the initial and ongoing treatment of seizures in dogs and cats for decades. PB is a relatively safe, effective, and inexpensive anticonvulsant drug. It has a high bioavailability and is rapidly absorbed, with peak plasma concentration 4 to 8 hours after oral administration. An appropriate starting dose is 2.5 mg/kg given orally twice a day.

After 2 weeks of therapy the animal should be examined and its morning prepill (trough) blood PB concentration determined. The trough serum PB concentration should be in the therapeutic range of 25 to 35  $\mu$ g/ml (107 to 150  $\mu$ mol/ L) in dogs and 10 to 30  $\mu$ g/ml (45 to 129  $\mu$ mol/L) in cats. If the serum concentration is too low, the dose of PB should be increased by approximately 25% (see Box 67-6) and the trough serum concentration determined again 2 weeks later. If the serum concentration is still inadequate, the dose of PB should be increased in 25% increments every 2 weeks while the blood concentration is monitored. Once the measured blood concentration of PB is adequate, the dog or cat should be observed through two or three cycles of seizures, and if control is determined to be acceptable, therapy is maintained at that dosage. Long-term dosing of PB can be complicated by the drug's induction of hepatic microsomal enzyme activity, increasing its own elimination and necessitating dosage increases. Blood PB concentrations should be reevaluated routinely every 6 months, 2 weeks after any change in dosage, and whenever two or more seizures occur between scheduled PB evaluations. Serum separator tubes should not be used to collect serum for this purpose because their use will underestimate the concentration of PB.

PB is well tolerated in most dogs at therapeutic serum concentrations. Sedation, depression, and ataxia may be pronounced for the first 7 to 10 days of therapy, but these adverse effects resolve with time (10 to 21 days) as the animal acquires a tolerance for the sedative effects of the drug. Transient (7 days) hyperexcitability can occur as an idiosyncratic effect in up to 40% of dogs and cats. The most common persistent adverse effects of PB include polyuria, polydipsia, and polyphagia. Owners should be advised to refrain from overfeeding animals receiving this anticonvulsant, even though their pet seems ravenous. Many animals acquire a dependence on the drug, and sudden withdrawal of the drug can precipitate seizures; therefore it is important for owners to administer the drug consistently once treatment is started.

Immune-mediated neutropenia or thrombocytopenia has been recognized in a few dogs within the first 6 months of starting PB, but these blood dyscrasias resolve when the PB is discontinued. PB administration may also be a risk factor for the development of superficial necrolytic derma-

titis in dogs. The most life-threatening potential complication of PB therapy is drug-induced hepatotoxicity. PB is a potent inducer of hepatic enzymes, and mild to moderate elevations in serum alkaline phosphatase (ALP) and alanine transaminase (ALT) activities are seen in virtually all dogs receiving the anticonvulsant. Significant hepatotoxicity is uncommon but is most likely to occur when peak serum PB concentrations are at the high end of the therapeutic range (>35 µg/ml; >150 µmol/L). Clinical features of significant hepatotoxicity include anorexia, sedation, ascites, and occasionally icterus. Laboratory testing typically reveals a large increase in ALT, decreased serum albumin, and abnormal bile acids. When hepatotoxicity is discovered, the patient should be rapidly switched to an alternative anticonvulsant and supportive measures initiated for liver failure. All animals receiving chronic PB therapy should be evaluated every 6 months to assess the effectiveness of the drug regimen, the serum concentration of PB, liver enzyme activities, and liver function.

PB increases the biotransformation of drugs metabolized by the liver, decreasing the systemic effects of many drugs administered concurrently. PB also increases the rate of thyroid hormone elimination, decreasing measured serum total and free T<sub>4</sub> and increasing serum thyroid-stimulating hormone concentrations, but this is rarely associated with clinical signs of hypothyroidism (see Chapter 51). Drugs that inhibit microsomal enzymes (e.g., chloramphenicol, tetracycline, cimetidine, ranitidine, enilconazole) may dramatically inhibit the hepatic metabolism of PB, resulting in increased serum concentrations of PB and potentially causing toxicity.

Seizures are controlled in 70% to 80% of dogs and most cats treated with PB monotherapy if serum PB concentrations are maintained within the target range. If seizures continue to occur at an unacceptable frequency or severity despite adequate serum concentrations, therapy with additional drugs must be considered.

### POTASSIUM BROMIDE

Control of refractory seizures can be improved through the addition of potassium bromide (KBr) to already established PB therapy in animals with poorly controlled seizures despite adequate serum concentrations of PB, decreasing seizure numbers by 50% or more in approximately 70% to 80% of dogs (see Box 67-6). KBr is also effective as a single agent and is considered by many to be the initial drug of choice in dogs with hepatic dysfunction and dogs that do not tolerate PB. KBr monotherapy is also commonly administered to large dogs with idiopathic epilepsy and a low frequency of seizures. The drug should not be administered to cats because of a high prevalence of drug-associated severe progressive bronchitis in that species. Bromide is excreted unchanged by the kidney. It is not metabolized by the liver and does not cause hepatotoxicity. Potassium bromide is typically administered as the inorganic salt dissolved in double distilled water to achieve a concentration of 200 to 250 mg/ml. Administration of the salt in gelatin capsules is also possible, but the concentrated drug in this form often causes gastric

irritation and vomiting. Dietary chloride should remain constant in dogs treated with KBr because high chloride intake (e.g., chips, rawhide bones) results in increased renal excretion of KBr and decreased serum concentrations. An appropriate starting dose of KBr is 20 mg/kg orally twice daily for monotherapy and 15 mg/kg orally twice daily when used as an add-on drug to PB. KBr serum concentrations should be measured 1 month after initiating therapy, 8 to 12 weeks later when a steady state is achieved, and then annually. The goal is to achieve a serum concentration of 2.5 to 3.0 mg/ml (25 to 30 mmol/L) of KBr when used as monotherapy and 1.0 to 2.0 mg/ml (10 to 20 mmol/L) when used together with PB. Serum PB concentrations should also be maintained in the midtherapeutic range in animals receiving KBr and PB.

When maintenance doses of KBr are administered, there is a long lag period between the initiation of treatment and achieving steady-state serum concentrations. KBr is therefore not recommended as monotherapy in dogs with frequent seizures in which rapid control is required. If KBr must be administered as the only anticonvulsant therapy in a dog with a severe or progressive seizure disorder or in a dog that must be switched from PB to KBr because of toxicity, it is possible to achieve therapeutic serum concentrations of KBr rapidly using a loading-dose protocol. Oral loading can be accomplished by administering 30 mg/kg of KBr orally four times a day for 5 days with food, followed by the administration of maintenance doses.

Adverse effects of KBr include polyuria, polydipsia, and polyphagia, but these may be less dramatic than the changes induced by PB therapy. Transient sedation, incoordination, anorexia, and constipation can also occur. Reversible limb stiffness, lameness, and muscle weakness will occur if serum bromide levels are excessive. Vomiting is a very common problem caused by gastric irritation from the hyperosmolality of the drug; this toxicity can be diminished by further splitting the daily dose (into four equal doses administered approximately every 6 hours) and by feeding a small amount of food with each dose. Pancreatitis occurs rarely. Dramatic sedation can occur in dogs being concurrently treated with PB; this is usually temporary but can be decreased by lowering the dose of PB administered by 25% or by administering intravenous saline to increase the renal excretion of KBr, keeping in mind that dramatically lowering the serum concentration of either drug may cause increased seizure activity. Biochemical abnormalities are not common in dogs treated with KBr monotherapy, but because some laboratory assays cannot distinguish bromide from chloride, there may be an artifactual increase in measured chloride.

### DIAZEPAM

Diazepam (Valium; Roche) is of limited use as a primary anticonvulsant in dogs because of its expense, its very short half-life, physical dependence, and the rapid development of tolerance to its anticonvulsant effects. Oral diazepam has been shown to be of some benefit for the long-term management of seizures in cats because tolerance to its anticonvul-

sant effect does not seem to occur in that species. Diazepam can be administered orally (0.3 to 0.8 mg/kg q8h) to achieve trough blood concentrations of 200 to 500 ng/ml. The drug is eliminated by hepatic metabolism, and the only common adverse effect is sedation, although idiosyncratic severe, lifethreatening hepatotoxicity has been documented in a few cats receiving daily diazepam for 5 to 11 days. This potentially fatal reaction warrants close owner observation of appetite and attitude and periodic monitoring of liver enzymes in all cats treated with diazepam. PB is a better choice for chronic anticonvulsant therapy in cats.

Diazepam also has a place in the emergency management of seizures and in the at-home treatment of dogs with idiopathic epilepsy experiencing cluster seizures. In dogs with a recognizable preictal phase or an aura preceding the seizure, an injectable preparation of diazepam (5 mg/ml) can be administered rectally (2 mg/kg) by the owner at the onset of these premonitory signs. Alternatively, this dose can be administered just after each observed seizure, with a maximum of three doses in 24 hours (each dose separated by at least 10 minutes). At-home rectal administration of diazepam decreases the occurrence of cluster seizures and the development of status epilepticus as well as dramatically decreasing the need for owners to seek expensive emergency treatment for their epileptic dogs. Diazepam dispensed for at-home rectal administration should be stored in a glass vial because plastic will adsorb the drug, decreasing its effectiveness. For administration the drug can be drawn into a syringe and injected through a 1-inch plastic teat cannula or rubber catheter directly into the rectum.

### **CLORAZEPATE**

Clorazepate (Traxene; Abbott Laboratories) is a benzodiazepine with a slightly more prolonged action than that of diazepam. This drug is effective as a sole anticonvulsant or when administered as an add-on drug. Chronic administration can result in tolerance to its antiseizure effects, potentially making all benzodiazepines ineffective for emergency use. The only recognized adverse effects are sedation, ataxia, and polyphagia, although acute hepatic necrosis might be a concern in cats because of shared metabolites with diazepam. There is also a potential for severe withdrawal seizure activity with this drug. The starting dose is 1 to 2 mg/kg, administered orally q12h, with desired therapeutic concentration of 300 to 500 ng/ml. Clorazepate administration to dogs being chronically treated with PB will increase serum PB concentrations, requiring monitoring and dosage adjustments.

### **FELBAMATE**

Felbamate (Felbatol; Wallace) is an effective anticonvulsant in dogs when used alone or as an add-on drug in dogs refractory to anticonvulsant therapy with PB and KBr. Following urinary excretion of 70% of the orally administered dose, Felbamate is metabolized by hepatic microsomal P450 enzymes. The recommended starting dose is 15 mg/kg q8h. Felbamate appears to have a wide margin of safety, and the daily dose can be increased in 15 mg/kg increments until the

seizures are adequately controlled, with reports of dosages as high as 70 mg/kg q8h without toxicity. Felbamate is an unusual anticonvulsant in that it does not cause sedation. Because approximately 30% of dogs treated with felbamate as an add-on drug with PB develop hepatotoxicity, monitoring of biochemistry panels and liver function tests is recommended. Aplastic anemia has been reported in humans receiving this drug but has not been documented in dogs. Serial monitoring of CBC and serum biochemistry panel is recommended at 1 month and every 3 months during treatment. Trough serum concentrations between 25 and 100 mg/L are reported to be therapeutic.

### **GABAPENTIN**

Gabapentin (Neurontin; Parke-Davis) is a structural analog of GABA, with a poorly understood mechanism of action. The drug is rapidly absorbed and renally excreted with some hepatic metabolism. The elimination half-life in dogs is very short (3 to 4 hours), requiring dosing every 6 to 8 hours. Moreover, the drug has a very high therapeutic index and very little potential for drug-drug interaction. Starting doses of 10 to 20 mg/kg q8h have been recommended. The dose should be increased gradually as needed (up to 80 mg/kg q6h) to avoid excessive sedation, which is the only reported adverse effect. Serum concentrations are rarely monitored, but the suspected therapeutic range for dogs is 4 to 16 mg/L. Preliminary clinical evaluation of gabapentin as an add-on drug in dogs with refractory epilepsy has recorded decreased seizure frequency in 50% of cases.

### **ZONISAMIDE**

Zonisamide (Zonegran; Elan) is a sulfonamide-based anticonvulsant that suppresses epileptic foci and blocks the propagation of epileptic discharges. This drug is well absorbed and hepatically metabolized, with a relatively long half-life (15 hours) in dogs not concurrently receiving PB or other drugs that induce microsomal enzymes. Zonisamide is effective as a sole agent or as an add-on drug. Mild adverse effects reported include sedation, ataxia, vomiting, and inappetence. The initial starting dose is 5 mg/kg twice daily in dogs not receiving PB and 10 mg/kg twice daily in dogs receiving concurrent PB. A serum concentration of 10 to 40 µg/ml is reported to be therapeutic.

### **LEVITIRACETAM**

Levitiracetam (Keppra) is a new anticonvulsant that is well tolerated and effective in human patients. The drug is well absorbed and rapidly metabolized, with a half-life of 3 to 4 hours in dogs. Most of the drug is excreted unchanged in the urine, and the remainder is metabolized by hydrolysis in multiple organs, with no significant hepatic metabolism. Limited information is available on its use in dogs and cats, but it reportedly decreases seizure frequency by over 50% in epileptic dogs when used as an add-on drug and has also been effective in cats with refractory seizures. A starting dose of 20 mg/kg q8h is recommended, with some reports of administration of much higher doses without toxicity.

Adverse effects include minimal sedation and salivation and vomiting in a few dogs.

### ALTERNATIVE THERAPIES

Approximately 20% to 25% of dogs treated for epilepsy using standard anticonvulsant therapy are never well controlled, despite attempts at therapeutic drug monitoring and appropriate dose adjustments. It is important to evaluate poorly controlled animals for underlying metabolic or intracranial disease that could be specifically treated. Alternative treatments should also be considered in these animals, including hypoallergenic diets, acupuncture, surgical division of the corpus callosum, and vagus nerve stimulation.

# EMERGENCY THERAPY FOR DOGS AND CATS IN STATUS EPILEPTICUS

Status epilepticus is a series of seizures or continuous seizure activity lasting for 5 minutes or longer without periods of intervening consciousness. Status epilepticus increases arterial blood pressure, body temperature, heart rate, cerebral blood flow, and cerebral oxygen consumption. It also decreases blood pH (because of lactic acidosis) and may decrease effective ventilation. As seizures continue, metabolic deterioration, increased intracranial pressure, acidosis, hyperthermia, and cardiac dysrhythmias are common, leading to progressive cerebral ischemia and neuronal death. Permanent neurologic damage and even death can result.

Status epilepticus is always a medical emergency. The most common reasons for a known idiopathic epileptic patient to present in status include poor chronic seizure control of cluster seizures and abrupt withdrawal of anticonvulsant medications (missed doses). Nonepileptics may present in status as a result of various metabolic (e.g., hypoglycemia, hypocalcemia, hepatic encephalopathy, hyperosmolality, renal failure, intoxications) and intracranial (e.g., neoplasia, trauma, infarct, malformation, heat stroke, granulomatous meningoencephalitis, infectious meningoencephalitis) disorders. History and physical examination findings help determine the cause of status epilepticus in an individual patient. Diagnostic testing for metabolic causes of seizures (especially hypoglycemia, hypocalcemia, electrolyte disturbances) should always be performed and specific treatment initiated when warranted. When intoxication is suspected, treatment should be directed at reducing further absorption of the toxin, increasing toxin excretion, and controlling the neurologic manifestation of seizures (see Box 67-4).

The goals of treatment are to stabilize the animal, stop the seizure activity, protect the brain from further damage, and allow recovery from the systemic effects of prolonged seizure activity. Oxygen is administered, as well as fluid therapy and supportive care, to minimize systemic effects. Diazepam is administered (intravenously or rectally) to stop the seizures; this is followed by phenobarbital to prevent seizure recur-



BOX 67-7

### Status Epilepticus Treatment in Dogs and Cats

- 1. If possible, insert an IV catheter.
- 2. Administer diazepam 2.0 mg/kg rectally if no IV access. If IV access is possible, administer 1.0 mg/kg intravenously. Repeat every 2 minutes if ineffective or if seizures recur. Administer maximum of four doses if necessary. If patient responds to diazepam administration but seizures recur, consider a diazepam CRI (1.0 mg/kg/h) in 0.9% saline or in D₅W. Continue the CRI for at least 6 hours; if no seizures occur, can then taper by 25%/h.
- Administer a loading dose of phenobarbital to prevent further seizures (5 mg/kg slow intravenously or intramuscularly twice, 10 minutes apart). This will take 20 to 30 minutes for maximum effect. Repeat 5 mg/kg dose q6h intramuscularly until oral dosing can be performed.
- 4. If seizures have not responded to diazepam or to the initial dose of phenobarbital, it will be necessary to stop the seizures using either:

- Sodium pentobarbital (3 to 15 mg/kg, intravenously slowly to effect)
- Repeat as needed (q4-8h) or maintain on CRI: (1.0-5.0 mg/kg/h to effect) in saline

or

Propofol (4 mg/kg, intravenously slowly over 2 minutes). Maintain on a CRI (0.10-0.25 mg/kg/minute). Maintain anesthesia for 6 to 12 hours, then taper CRI by 25% every 2 to 4 hours to recover.

- 5. Maintain a patent airway and monitor respirations.
- 6. Initiate IV fluids (maintenance rate).
- Assess body temperature. If >41.4°C (>105°F), cool with cool-water enemas.
- If hyperthermic or if seizure activity was prolonged (>15 minutes), administer:
   mannitol: 1.0 g/kg, intravenously over 15 minutes
   furosemide: 2 mg/kg, intravenously

IV, Intravenous; CRI, constant rate infusion.

rence. More aggressive treatment is required if seizures continue, usually involving a propofol or pentobarbital infusion to stop seizure activity. Mannitol and furosemide are also recommended (as for head trauma, Box 65-2) to decrease the brain edema secondary to prolonged seizure activity. Details regarding the treatment of status epilepticus are outlined in Box 67-7.

### Suggested Readings

Barnes HL et al: Clinical signs, underlying cause and outcome in cats with seizures: 17 cases (1997-2002), *J Am Vet Med Assoc* 225:1723, 2004.

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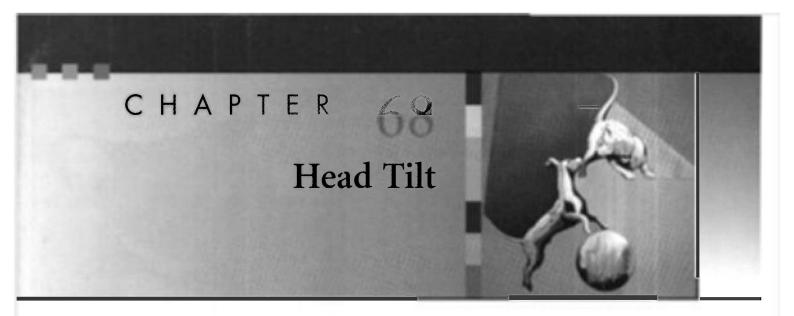
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### CHAPTER OUTLINE

GENERAL CONSIDERATIONS LOCALIZATION OF THE LESION

Peripheral and Central Vestibular Disease Peripheral Vestibular Disease Central Vestibular Disease Paradoxical Vestibular Disease PERIPHERAL VESTIBULAR DISEASE

Disorders Causing Peripheral Vestibular Signs BILATERAL PERIPHERAL VESTIBULAR DISEASE CENTRAL VESTIBULAR DISEASE Metronidazole Toxicity

ACUTE VESTIBULAR ATTACKS

### **GENERAL CONSIDERATIONS**

Head tilt is a common neurologic abnormality in dogs and cats. It indicates a lesion of the vestibular system, which consists of central and peripheral parts.

The peripheral vestibular system includes sensory receptors for vestibular input located in the membranous labyrinth of the inner ear within the petrous temporal bone of the skull and the vestibular portion of the vestibulocochlear nerve (CN8), which carries information from these receptors to the brainstem. The central vestibular structures include the brainstem vestibular nuclei and pathways in the medulla oblongata and the flocculonodular lobe of the cerebellum (Fig. 68-1). Abnormalities involving the central or peripheral vestibular system typically cause head tilt, circling, ataxia, rolling, and nystagmus.

Nystagmus is defined as an involuntary rhythmic oscillation of the eyeballs. In the jerk nystagmus typical of vestibular disease the eye movements have a slow phase in one direction and a rapid recovery in the opposite direction. Jerk nystagmus direction is defined as the direction of the fast phase. Less common than jerk nystagmus is pendular nystagmus, a slight oscillatory movement of the eyeballs with no slow or fast phase; this condition is most often seen in

Siamese, Birman, and Himalyan cats because of a congenital abnormality of the visual pathway.

### LOCALIZATION OF THE LESION

Head tilt indicates vestibular dysfunction. The first step in a patient with a head tilt should always be an attempt to localize disease to either the central or the peripheral components of the vestibular system (Box 68-1). The clinician can usually accomplish this goal with a careful physical and neurological examination.

# PERIPHERAL AND CENTRAL VESTIBULAR DISEASE

Severe problems of balance resulting in ataxia, incoordination, falling, and rolling are prominent in animals with either central or peripheral vestibular disease. The head tilt (ear pointed toward the ground) is typically on the same side as the lesion, and tight circling toward that side is common. Ipsilateral strabismus may be seen when the nose is elevated. Vomiting, salivation, and other signs of motion sickness are often apparent.

Nystagmus observed when the head is held motionless is called *spontaneous nystagmus* or *resting nystagmus*. Nystagmus that develops only when the head is held in an unusual position is called *positional nystagmus*. Some animals with compensated vestibular disease (either central or peripheral) do not have detectable spontaneous nystagmus but develop positional nystagmus when they are rolled over on their back (see Fig. 63-23). Nystagmus in a patient with peripheral vestibular disease is always either horizontal or rotary, and although the intensity of nystagmus may change when the head is held in different positions, the direction will not. The nystagmus in animals with central vestibular diseases can be horizontal, rotary, or vertical and may change direction as the position of the head is changed.

### PERIPHERAL VESTIBULAR DISEASE

Animals with peripheral vestibular disease should have normal mentation and consciousness. They have normal

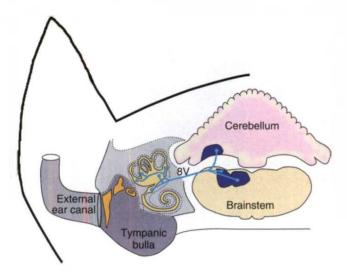


FIG 68.1

Anatomy of the central and peripheral vestibular system. Sensory receptors for vestibular input are located in the membranous labyrinth of the inner ear. Input from these receptors enters the brain via the vestibular portion of CN8 (8V), and fibers terminate in central vestibular nuclei in the brainstem and cerebellum.

strength and postural reactions, although these tests may be difficult to assess because affected animals have impaired balance and a tendency to fall and roll. Spontaneous and positional nystagmus is horizontal or rotary or alternates between the two and will not change fast-phase direction when the animal is held in multiple positions or examined repeatedly during the day. Damage to inner ear receptors or the axons of CN8 results in vestibular dysfunction and sometimes deafness. Disorders that affect both the middle and inner ear will sometimes damage the axons of the facial nerve (CN 7) and the sympathetic innervation to the eye, resulting in concurrent facial nerve paralysis, Horner's syndrome, and peripheral vestibular dysfunction (Fig. 68-2).

### CENTRAL VESTIBULAR DISEASE

Early in the course of disease, animals with central vestibular dysfunction may not have clinical features that readily distinguish them from animals with peripheral vestibular dysfunction. With time and progression, however, they usually develop additional signs indicating brainstem involvement. Mentation may be dull or depressed or behavior may be altered as the ascending reticular activating system is disrupted. Ipsilateral paresis and postural reaction deficits (abnormal knuckling, hopping) develop on the side of the lesion as the upper motor neuron pathways to the limbs are involved, and affected animals may lose the ability to walk. Although spontaneous nystagmus can be in any direction, a vertical nystagmus or a nystagmus that changes directions with different head positions indicates central vestibular disease. The presence of cranial nerve abnormalities other than facial nerve paralysis and Horner's syndrome in an animal with vestibular signs usually indicates central (i.e.,



FIG 68-2
Adult cat with peripheral vestibular disease and Horner's syndrome on the left side caused by otitis media-interna.



BOX 68-

Vestibular Disease Clinical Findings

### Central and Peripheral Vestibular Disease

Incoordination, loss of balance
Head tilt toward lesion
Circling/falling/rolling toward the side of the lesion
+/- ventral strabismus on side of lesion
Vomiting, salivation
Spontaneous nystagmus (fast phase away from lesion)
Nystagmus may be positional

### Peripheral Vestibular Disease

Nystagmus always horizontal or rotary
No change in nystagmus direction
Postural reactions and proprioception normal
With middle/inner ear disease, may see concurrent CN7
deficit and Horner's syndrome
No other cranial nerve deficits

### **Central Vestibular Disease**

Occasionally indistinguishable from peripheral disease Findings that confirm disease as central:

Vertical nystagmus
Nystagmus that changes direction with head position
Abnormal postural reactions on side of lesion

Multiple cranial nerve deficits

### Paradoxical Vestibular Syndrome (Cerebellar Lesion)

Head tilt and circling away from side of lesion
Fast phase nystagmus toward the lesion
May exhibit vertical nystagmus
Abnormal postural reactions on side of lesion
+/- Multiple cranial nerve deficits on side of lesion
+/- Hypermetria, truncal sway, and head tremor

brainstem) disease. Neoplasms or granulomas located at the cerebellomedullary angle often result in simultaneous dysfunction of the vestibular (CN8), facial (CN7), and trigeminal (CN5) nerves, so the trigeminal nerve (i.e., facial and nasal sensation) should always be assessed in animals with vestibular signs.

### PARADOXICAL VESTIBULAR SYNDROME

Vestibular signs can be seen with lesions affecting the caudal cerebellar peduncle or the flocculonodular lobe of the cerebellum. This syndrome is called paradoxical vestibular syndrome because affected animals have a head tilt and circling away from the lesion and a fast phase nystagmus directed toward the lesion. Postural reaction deficits, when present, are on the side of the lesion and are therefore the most reliable clinical feature allowing lesion localization. Other signs of cerebellar dysfunction, such as hypermetria, truncal sway, and head tremor, are often seen. Diagnostic evaluation is the same as that for central vestibular disease and other intracranial disorders (see Chapter 65).

### PERIPHERAL VESTIBULAR DISEASE

Peripheral vestibular disease is much more common in dogs and cats than central disease and generally carries a better prognosis. The most common disorders causing peripheral vestibular signs are infection, polyps, or neoplasia affecting the middle and inner ear and transient idiopathic vestibular syndromes. Peripheral vestibular disease can also occur as a congenital problem; as a result of trauma; and, rarely, as a result of aminoglycoside-induced receptor degeneration (Box 68-2). Peripheral vestibular signs with or without facial nerve paralysis have also been seen in hypothyroidassociated polyneuropathy in dogs.

Diagnostic evaluation of patients with peripheral vestibular signs should include a thorough otoscopic examination and external palpation of the bullae for asymmetry or pain. Ototoxic drugs or treatments should be discontinued and systemic evaluation for inflammatory or metabolic disease performed. Radiographs, computed tomography (CT), or magnetic resonance imaging (MRI) of the tympanic bullae (middle ear) should be evaluated with the patient under general anesthesia before ear flushing is performed. When warranted, a myringotomy can then be used to collect a sample from the middle ear for cytological analysis and culture.

### DISORDERS CAUSING PERIPHERAL **VESTIBULAR SIGNS** Otitis Media-Interna

Otitis media-interna (OM-OI) is one of the most common causes of peripheral vestibular signs in dogs and cats. Concurrent facial nerve paralysis or Horner's syndrome affecting the same side is sometimes apparent (Fig. 68-3; see also Fig. 68-2). All dogs and cats with peripheral vestibular disease should be evaluated for ear disease. Most animals with OM-



BOX 68-2

Disorders Causing Head Tilt

### Central Vestibular Disease

Trauma or hemorrhage Infectious disorders Granulomatous meningoencephalitis (dogs) Neoplasia Vascular infarct Thiamine deficiency Metronidazole intoxication

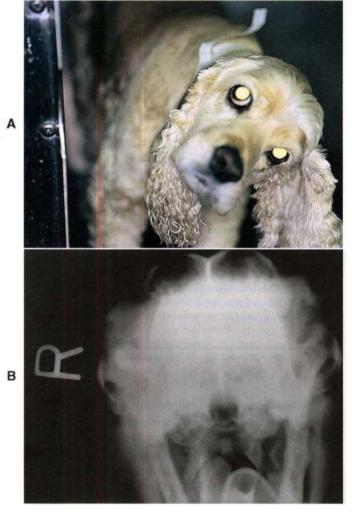
### Peripheral Vestibular Disease

Otitis media-interna Middle ear tumors/feline nasopharyngeal polyps Trauma Congenital vestibular syndromes Geriatric canine vestibular disease Feline idiopathic vestibular syndrome Aminoglycoside ototoxicity Chemical ototoxicity Hypothyroidism(?)

OI have obvious otitis externa, and many have a tympanic membrane that appears abnormal or ruptured. Occasionally, the otoscopic examination is normal.

Skull radiographs can be evaluated for changes in the tympanic bullae suggesting chronic inflammatory disease, trauma, or tumor. Ventrolateral, oblique, lateral, and openmouth radiographs of the skull should be performed with the patient under general anesthesia. Radiographic evidence of OM-OI includes increased thickness of the bones of the tympanic bullae and petrous temporal bone and increased fluid or soft-tissue density within the tympanic bullae (see Figs. 71-7 and 68-3). Because radiographs may be normal with acute infections, more sensitive advanced imaging techniques (CT and MRI) are recommended if radiographs are nondiagnostic.

While the animal is sedated or anesthetized, a culture should be obtained from the external ear canal and the ear canal and the tympanic membrane should be carefully examined using an otoscope or a small endoscope. If imaging suggests that fluid is present within the middle ear, a sample of that fluid should be collected for cytology and culture. If the tympanic membrane is ruptured, the sample can be obtained directly under visualization. If the tympanic membrane appears to be intact, the external ear canal can be cleaned by flushing with warm 0.9% saline until the fluid obtained is clear, and then a myringotomy may be performed. Using a 22-gauge, 3.5-inch spinal needle attached to a 6-ml syringe, the clinician punctures the tympanic membrane just caudal to the malleus at the 6 o'clock position and gently aspirates fluid from the middle car into the syringe. If fluid is not obtained, 0.5 to 1.0 ml of sterile saline can be instilled and then aspiration can be repeated. After the diag-



**FIG 68-3 A,** Adult Cocker Spaniel with left peripheral vestibular disease caused by otitis media-interna. **B,** Radiograph reveals thickening of the left bulla wall with an increase in density within the bulla. Osteotomy of the ventral bulla revealed bilateral otitis media-interna.

nostic sample is obtained, the middle ear should be flushed repeatedly with sterile saline to remove exudate from the bulla.

Medical treatment of dogs and cats with bacterial OM-OI consists of a 4- to 6-week course of systemic antibiotics, with the choice of antibiotic based on culture and sensitivity results. Pending culture results, antibiotic treatment can be initiated using a broad-spectrum antibiotic such as a first-generation cephalosporin (cephalexin, 22 mg/kg, administered orally q8h), a combination of amoxicillin and clavulanic acid (Clavamox, 12.5 to 25 mg/kg, administered orally q8h), or enrofloxacin (5 mg/kg, administered orally q12h). If conservative treatment does not resolve the infection or if there is radiographic evidence of chronic bone changes in the bulla, ventral bulla osteotomy should be performed, followed by a course of antibiotic therapy. Early recognition of OM-OI and prompt initiation of appropriate therapy result





**FIG 68-4 A** and **B**, A 12-year-old Golden Retriever with head and body tilt caused by geriatric canine vestibular disease.

in a good prognosis for recovery. The facial nerve paralysis may be permanent in spite of treatment. Failure to treat OM-OI aggressively can result in ascent of the infection up the nerves into the brainstem, resulting in neurologic deterioration, central vestibular signs, and often death.

### **Geriatric Canine Vestibular Disease**

Geriatric canine vestibular disease (i.e., old dog vestibular disease), an idiopathic syndrome, is the most common cause of acute unilateral peripheral vestibular dysfunction in old dogs, with a mean age of onset of 12.5 years. The disorder is characterized by the very sudden onset of head tilt, loss of balance, and ataxia with a horizontal or rotatory nystagmus (Fig. 68-4). Proprioception and postural reactions are normal, although they may be difficult to assess. Facial paresis and Horner's syndrome are not present, and no other neurologic abnormalities are observed. Approximately 30%

of affected dogs have transient nausea, vomiting, and anorexia.

Any older dog with a peracute onset of unilateral peripheral vestibular disease with no other neurologic abnormalities should be suspected to have geriatric canine vestibular disease. A careful physical examination, neurologic examination, and otoscopic examination should be performed. Further extensive diagnostic testing is often delayed for a few days while the dog is supported and monitored for improvement.

The diagnosis of geriatric canine vestibular disease is based on the signalment, neurologic findings, exclusion of other causes of peripheral vestibular dysfunction, and alleviation of clinical signs with time. The spontaneous nystagmus usually resolves within a few days and is replaced by a transient positional nystagmus in the same direction. The ataxia gradually abates during 1 to 2 weeks, as does the head tilt. Occasionally, the head tilt is permanent.

The prognosis for recovery is excellent; no therapy is recommended. When vomiting is severe, H1 histaminergic receptor antagonists (diphenhydramine, 2 to 4 mg/kg, administered subcutaneously 98h), M1 cholinergic receptor antagonists (chlorpromazine, 1 to 2 mg/kg, administered orally 98h), or vestibulosedative drugs (meclizine, 1 to 2 mg/ kg, administered orally q24h) can be administered for 2 to 3 days to alleviate the emesis associated with motion sickness. Recurrent attacks are unusual but may occur on the same side or on the opposite side.

### Feline Idiopathic Vestibular Syndrome

Feline idiopathic vestibular syndrome is an acute, nonprogressive disorder similar to the idiopathic geriatric vestibular syndrome that occurs in dogs. It is a common disorder affecting cats of any age. The disease may be more prevalent in the summer and early fall and in certain geographic locations, particularly the northeastern United States, suggesting a possible role for an infectious or parasitic cause. This syndrome is characterized by the peracute onset of peripheral vestibular signs, such as severe loss of balance, disorientation, falling and rolling, a head tilt, and spontaneous nystagmus, with no abnormalities of proprioception or in other cranial nerves. The diagnosis is based on the clinical signs and the absence of ear problems or other disease. If radiographs of the tympanic bullae and petrous temporal bone are obtained, the findings are normal, as are the results of cerebrospinal fluid (CSF) analysis. Spontaneous improvement is usually seen within 2 to 3 days, with a complete return to normal within 2 to 3 weeks.

### Neoplasia

Tumors involving the inner and middle ear may damage peripheral vestibular structures and result in peripheral vestibular dysfunction. Tumors can arise from regional soft tissues (e.g., squamous cell carcinoma, adenocarcinoma, lymphoma) or from the osseous bulla (e.g., fibrosarcoma, chondrosarcoma, osteosarcoma). Tumors originating within the external ear canal (e.g., squamous cell carcinoma, ceruminous gland adenocarcinoma) may also invade past the tympanic membrane to involve the middle and inner ear. Less commonly, tumors of CN8 (e.g., neurofibroma or neurofibrosarcoma) result in peripheral vestibular dysfunction.

When tumors are located in the middle and inner ear, facial nerve paralysis or Horner's syndrome commonly accompanies peripheral vestibular signs. Radiographic evidence of soft-tissue density within the bullae and associated bone lysis suggests tumor. Advanced imaging with CT or MRI provides additional detail and determines whether the tumor has invaded the cranial vault. Diagnosis can be confirmed by biopsy. The invasive nature of tumors in this location makes total resection difficult. Radiotherapy or chemotherapy may be beneficial in some animals (see Chapters 76 and 77).

### Nasopharyngeal Polyps

Nasopharyngeal inflammatory polyps originate at the base of the eustachian tube in kittens and young adult cats and grow passively into the nasopharynx, nose, or middle ear. Most affected cats exhibit stertorous breathing or nasal discharge as a result of respiratory obstruction by these polyps, but cats with polyps in the middle and inner ear are presented with peripheral vestibular signs and sometimes Horner's syndrome and facial nerve paralysis. Otoscopic examination is often normal, although bulging of the tympanic membrane or extension of a polyp into the external ear canal is possible. A diagnosis of nasopharyngeal polyps should be suspected when a young cat is presented with concurrent peripheral vestibular dysfunction and nasopharyngeal obstruction. Skull radiographs reveal soft tissue within the bullae and thickening of the bone but no bone lysis. Surgical removal requires ventral bulla osteotomy, and the prognosis is excellent for cure if all abnormal tissue is removed (see Chapter 15).

### Trauma

Trauma to the middle and inner ear will result in peripheral vestibular signs and commonly concurrent Horner's syndrome and facial nerve paralysis. Facial abrasions, bruises, and fractures may be evident on initial examination. Hemorrhage in the external ear canal may be evident on an otoscopic examination. Radiographs or advanced diagnostic imaging will reveal the extent of the problem. Supportive treatment for head trauma and possible posttraumatic infection should be initiated. Vestibular signs usually resolve with time, whereas facial paralysis and Horner's syndrome may persist.

### **Congenital Vestibular Syndromes**

Purebred dogs and cats that show peripheral vestibular signs before 3 months of age are likely to have a congenital vestibular disorder. Congenital unilateral peripheral vestibular syndromes have been recognized in the German Shepherd Dog, Doberman Pinscher, Akita, English Cocker Spaniel, Beagle, Smooth Fox Terrier, and Tibetan Terrier as well as in

Siamese, Burmese, and Tonkinese cats. Clinical signs may be present at birth or develop during the first few months of life. Head tilt, circling, and ataxia may initially be severe; however, with time, compensation is common, and many affected animals make acceptable pets. The diagnosis is based on the early onset of signs. If ancillary tests such as radiography and CSF analysis are performed, findings are normal. Deafness may accompany the vestibular signs, particularly in the Doberman Pinscher, the Akita, and the Siamese cat.

### **Aminoglycoside Ototoxicity**

Aminoglycoside antibiotics rarely cause degeneration within the vestibular and auditory systems of dogs and cats. This ototoxicity is usually associated with the systemic administration of high doses or the prolonged use of these antibiotics, particularly in animals with impaired renal function. Degeneration within the vestibular system may result in unilateral or bilateral peripheral vestibular signs and loss of hearing. In most cases the vestibular signs resolve if therapy is discontinued immediately, but deafness may persist.

### **Chemical Ototoxicity**

Many drugs and chemicals are potentially toxic to the inner ear. If the integrity of the tympanic membrane is in doubt, topical otic products containing chlorhexidine, dioctyl-sulfo succinate (DOSS), or aminoglycosides should never be used. Warm saline or 2.5% acetic acid solutions should be used for flushing ears. Whenever vestibular dysfunction becomes evident immediately after instilling a substance in an ear canal, the product should be removed and the ear canal flushed with copious quantities of saline. Vestibular signs will usually resolve within a few days or weeks, but deafness may persist.

### **Hypothyroidism**

Vestibular dysfunction has occasionally been reported in association with hypothyroidism in adult dogs. Concurrent facial nerve paralysis may be seen. Other systemic signs of hypothyroidism, such as weight gain, poor haircoat, and lethargy, may or may not be present. Clinicopathologic testing may show abnormalities suggestive of hypothyroidism (e.g., mild anemia, hypercholesterolemia). The diagnosis is established through thyroid function testing (see Chapter 51). The response to replacement thyroid hormone is variable.

# BILATERAL PERIPHERAL VESTIBULAR DISEASE

Most animals with bilateral peripheral vestibular disease have no discernible head tilt. Affected animals have a widebased stance and are ataxic, usually ambulating in a crouched position with a wide side-to-side swinging of the head. Their conscious proprioception (knuckling) is normal. Affected animals have a definite balance problem, and they fall or circle to either side. No spontaneous or positional nystagmus is observed; in most cases normal vestibular eye movements are also lost. Affected animals are deaf if the cochlear portion of CN8 is also involved. When the animal is held suspended by the pelvis and lowered toward the ground, an affected animal may curl its head and neck toward the sternum instead of raising its head and extending the thoracic limbs toward the floor for weight bearing. Differential diagnoses considered in animals with bilateral vestibular disease include an idiopathic or congenital syndrome, trauma, ototoxicity, inner ear infections, and hypothyroidism. The diagnostic workup is the same as that used in dogs and cats with unilateral peripheral vestibular disease.

### CENTRAL VESTIBULAR DISEASE

Central vestibular disease is much less common in dogs and cats than peripheral vestibular disease and generally carries a poor prognosis. Central vestibular disease can be caused by any inflammatory, neoplastic, vascular, or traumatic disorders affecting the brainstem (see Box 68-2). In particular, granulomatous meningoencephalitis (dogs), Rocky Mountain spotted fever (dogs), and feline infectious peritonitis (cats) seem to have a predilection for this region of the brain. Dogs and cats with cerebellar infarcts and tumors are commonly presented with paradoxical vestibular signs.

A standard workup for intracranial disease is performed in animals that have central vestibular signs. A complete physical, neurologic, and ophthalmologic examination is essential to look for evidence of disease elsewhere in the body. Clinicopathologic testing and thoracic and abdominal radiography are warranted to search for neoplastic or infectious inflammatory systemic disease. Finally, advanced diagnostic imaging, particularly using MRI, and CSF collection and analysis should be considered. (See Chapter 65 for a more thorough discussion of the diagnostic approach taken in animals with intracranial disease.)

### METRONIDAZOLE TOXICITY

Central vestibular signs have been reported in dogs after administration of metronidazole (Flagyl; Pharmacia and Searle). Signs of metronidazole toxicity are most likely to develop when the drug is administered orally at high doses (usually >60 mg/kg/day) for 3 to 14 days. Initial signs include anorexia and vomiting, with rapid progression to ataxia and vertical nystagmus. The ataxia may be very severe, making walking impossible and resulting in a "bucking" gait. Seizures and head tilt occasionally occur. Treatment consists of stopping the medication and providing supportive care. The prognosis is good for recovery, but complete recovery may take 2 weeks. The administration of diazepam (0.5 mg/kg once intravenously and then orally q8h for 3 days) has been shown to dramatically speed recovery. Metronidazole toxicity has also been reported in cats receiving lower doses of metronidazole. Forebrain and cerebellar signs predominate in this species.

### ACUTE VESTIBULAR ATTACKS

A peracute onset of loss of balance, nystagmus, and severe ataxia that lasts only minutes is occasionally seen in dogs. Head tilt may be mild or absent. Neurologic examination during an episode is usually most consistent with peripheral disease, with no postural reaction deficits or cranial nerve abnormalities, but a few dogs have had vertical nystagmus, localizing to central vestibular disease. Dogs completely recover within minutes with no residual neurologic abnormalities and no obvious postictal signs. Some affected dogs have gone on to develop brain (especially cerebellar) infarcts, which suggests that these events could be transient ischemic attacks, as reported in humans. Other affected dogs progress to have recognizable epileptic seizures, which suggests that these events could represent seizure activity in some dogs. Intracranial mass lesions have been identified in a few affected dogs. Rarely, dogs have been reported to have intermittent episodic peripheral vestibular dysfunction with early OM-OI. Dogs with a history of acute vestibular attacks should have a careful physical and neurologic examination performed as well as systemic screening tests for inflammatory or neoplastic disease, disorders of coagulation, and hypertension. An otoscopic examination should be performed. Advanced diagnostic imaging (CT, MRI) to evaluate the middle ear and the brain may be warranted.

### Suggested Readings

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# CHAPTER Encephalitis, Myelitis, and Meningitis

### CHAPTER OUTLINE

GENERAL CONSIDERATIONS NECK PAIN

NON-INFECTIOUS INFLAMMATORY DISORDERS

Steroid-Responsive Meningitis-Arteritis Granulomatous Meningoencephalitis Necrotizing Meningoencephalitis Feline Polioencephalomyelitis

### INFECTIOUS INFLAMMATORY DISORDERS

Feline Immunodeficiency Virus Encephalopathy Bacterial Meningoencephalomyelitis

Canine Distemper Virus

Rabies

Feline Infectious Peritonitis

**Toxoplasmosis** 

Neosporosis

Lyme Disease

Mycotic Infections

Rickettsial Diseases

Parasitic Meningitis, Myelitis, and Encephalitis

### **GENERAL CONSIDERATIONS**

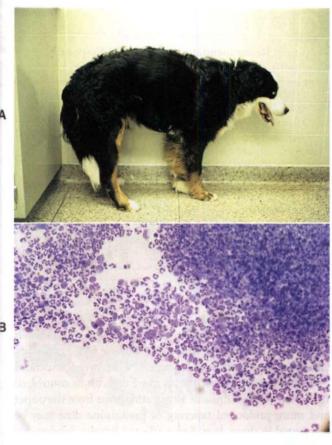
Bacterial, viral, protozoal, mycotic, rickettsial, and parasitic pathogens are all recognized as etiologic agents of inflammatory central nervous system (CNS) disease in dogs and cats. In addition, a variety of meningitis syndromes that have no identifiable etiology but are presumed to have an immunologic basis exist in dogs. These include a steroid-responsive meningitis-arteritis (SRMA) of young dogs, granulomatous meningoencephalomyelitis (GME), and necrotizing meningoencephalitis (NME).

The clinical signs of CNS inflammation vary and depend on both the anatomic location and the severity of inflammation. Individual syndromes may have characteristic constellations of clinical signs. Cervical pain and rigidity are common in dogs with meningitis of any etiology, causing a reluctance to walk, an arched spine, and resistance to passive manipulation of the head and neck (Fig. 69-1). Fever is common. Inflammation of the spinal cord (myelitis) will cause associated upper motor neuron (UMN) or lower motor neuron (LMN) deficits in the limbs, depending on the spinal cord region involved. Animals with inflammation in the brain (encephalitis) can experience vestibular dysfunction, seizures, hypermetria, or disorders of consciousness reflecting the distribution of intracranial lesions.

A thorough physical and ophthalmologic examination and search for systemic abnormalities should be performed. Dogs and cats with bacterial meningitis/meningoencephalitis usually have an infected site from which the infection has spread to the CNS. Animals with viral, protozoal, fungal, or rickettsial meningitis/meningoencephalitis may have involvement of other organs, such as the lung, liver, muscle, or eye, which may aid in diagnosis. Cerebrospinal fluid (CSF) analysis is necessary to confirm a suspected diagnosis of CNS inflammatory disease. Analysis of the cells found in the CSF, together with the clinical and neurologic findings, may aid in determining the etiology of the inflammation in an individual case (see Box 64-3). Analysis of CSF protein, CSF culture, measurement of serum and CSF antibody titers for likely infectious agents, and CSF polymerase chain reaction (PCR) analysis may also be of diagnostic value. These results, with the use of other appropriate ancillary diagnostic tests, allow diagnosis of a specific disorder and the initiation of prompt appropriate treatment (Table 69-1).

### **NECK PAIN**

Neck pain is a sign commonly associated with compressive or inflammatory diseases of the cervical spinal cord. Animals with neck pain typically have a guarded horizontal neck carriage and are unwilling to turn their neck to look to the side; they will instead pivot the entire body. As part of every routine neurologic examination, the presence or absence of cervical hyperesthesia should be assessed by deep palpation of the vertebrae and cervical spinal epaxial muscles and by resistance to flexion, hyperextension, and lateral flexion of the neck (Fig. 63-21). Anatomic structures that can cause



### FIG 69-1

**A,** A young Bernese Mountain Dog with steroid-responsive meningitis arteritis stands with an arched spine and is reluctant to walk because of pain. **B,** Cerebrospinal fluid from this dog is inflammatory, with a dramatic neutrophilic pleocytosis. (From Meric S et al: Necrotizing vasculitis of the spinal pachyleptomeningeal arteries in three Bernese Mountain Dog littermates, *J Am Anim Hosp Assoc* 22:463, 1986.)

neck pain include the meninges, nerve roots, intervertebral disks, joints, bones, and muscles. Neck pain has also been recognized as a clinical symptom of increased intracranial pressure, particularly as a result of forebrain mass lesions (Box 69-1).

# NON-INFECTIOUS INFLAMMATORY DISORDERS

# STEROID-RESPONSIVE MENINGITIS-ARTERITIS

SRMA is the most common form of meningitis diagnosed in most veterinary hospitals. An immunological cause is suspected, resulting in vasculitis/arteritis affecting the meningeal vessels throughout the entire length of the spinal cord and brainstem. This disorder has also been called *steroid-responsive suppurative meningitis*, necrotizing vasculitis, juvenile polyarteritis, pain syndrome, and aseptic meningitis. Affected dogs are usually juveniles or young adults (6 to 18



### **TABLE 69-1**

Ancillary Tests in the Diagnosis of Infectious Inflammatory Central Nervous System Disease

DISORDER SUSPECTED	ANCILLARY DIAGNOSTICS
Acute distemper (D)	Conjunctival scrapings
ricolo disionipor (b)	Ophthalmic exam
	Thoracic radiographs
	Skin biopsy immunohistochemistry
	RT-PCR blood, CSF
	CSF antibody titer
Bacterial (D, C)	Ear/throat/eye exam
240101141 (2), 0)	Thoracic radiographs
	Cardiac and abdominal
	ultrasound
	Spinal radiographs
	Skull CT or MRI
	Blood/urine cultures
	CSF culture
Toxoplasmosis (D, C)	Ophthalmic exam
	ALT, AST, CK activities
	CSF, serum titers
	PCR CSF, aqueous humor, blood,
	tissues
Neosporosis (D)	Ophthalmic exam
	AST, CK activities
	CSF, serum titers
	Muscle immunohistochemistry
Feline infectious	Ophthalmic exam
peritonitis (C)	Serum globulin
	Abdominal palpation/ultrasound
	Coronavirus antibody CSF, serum
	Coronavirus PCR CSF
Cryptococcosis (D, C)	Ophthalmic exam
71	Thoracic radiographs
	Brain MRI
	Nasal swab cytology
	Lymph node aspirates
	Test for capsular antigen in
	serum, CSF
	CSF culture
Rocky Mountain	Thoracic radiographs
spotted fever (D)	CBC, platelet count
	Serum globulin
	Skin biopsy: IFA
	Serum titer (demonstrate rise)
Ehrlichiosis (D)	CBC, platelet count
	Serum titer
	Ophthalmic exam

D, Dog; C, cat; RT-PCR, reverse-transcriptase polymerase chain reaction; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; PCR, polymerase chain reaction; CBC, complete blood count; IFA, immunofluorescent antibody analysis.



### Causes of Neck Pain in the Dog

MUSCLE: Myositis (immune, infectious), muscle injury BONE: Fracture/luxation, diskospondylitis, vertebral osteomyelitis, neoplasia

JOINT (facetal joints): Polyarthritis (immune, infectious), degenerative joint disease (osteoarthritis)

INTERVERTEBRAL DISK: Disk degeneration/prolapse

NERVE ROOT: Neoplasia, compression (by disk, tumor, fibrous tissue)

MENINGES: Neoplasia, inflammation (Immune, infectious)

BRAIN: Mass lesion (neoplasia, inflammatory)

months of age), but middle-aged and older dogs are occasionally affected. Large-breed dogs are most commonly affected. SRMA may be seen as a breed-associated syndrome in Beagles (Beagle pain syndrome), Bernese Mountain dogs, Boxers, German Shorthaired Pointers, and Nova Scotia Duck Tolling Retrievers. Clinical signs of SRMA include fever, cervical rigidity, and vertebral pain that may wax and wane early in the course of disease. Affected dogs are alert and systemically normal, with a common owner complaint being that the dog will not eat or drink unless the bowl is raised to head level. Neurologic deficits (e.g., paresis, paralysis, ataxia) are rare but can develop, particularly in chronically affected or inadequately treated dogs, as a result of concurrent myelitis, spinal cord hemorrhage, or infarction.

Laboratory changes typically include a neutrophilic leukocytosis with or without a left shift. Spinal fluid analysis shows an increased protein concentration and a neutrophilic pleocytosis (often >100 cells/µl; >75% neutrophils). Early in the course of the disease, when neck pain is intermittent, CSF may be normal or minimally inflammatory. Within 24 hours of administration of a single dose of prednisone, CSF may be normal or show a predominance of mononuclear cells; therefore CSF should always be collected for diagnosis when a dog is symptomatic before initiating therapy. High IgA concentrations are found in the CSF and serum of many dogs with SRMA, aiding diagnosis. Some dogs with SRMA have concurrent immune-mediated polyarthritis (IMPA). Bacterial cultures of the CSF and blood are negative. To date, no etiologic agent has been identified.

Treatment with corticosteroids consistently and rapidly alleviates the signs of fever and cervical pain. Dogs that are not treated early in the course of the disease occasionally develop neurologic deficits associated with spinal cord infarction and meningeal fibrosis; treatment may not resolve the resultant neurologic signs in these dogs. Corticosteroids should be administered initially at immunosuppressive dosages and then tapered to alternate-day therapy and decreasing dosages over a period of 4 to 6 months (Box 69-2). Dogs that do not respond completely to prednisone and dogs that relapse during prednisone tapering may benefit from the addition of azathioprine (Imuran; Burroughs Well-



### Treatment Recommendations for Steroid-Responsive Meningitis Arteritis

- 1. Prednisone 2 mg/kg q 12h orally for 2 days
- 2. Prednisone 2 mg/kg q 24h orally for 14 days
- 3. Assess clinical response

If clinical signs have resolved, the dose of prednisone is gradually tapered:

- 1 mg/kg q24h for 4 weeks
- 1 mg/kg q48h for 4 weeks
- 0.5 mg/kg q48h for 8 weeks

If clinical signs are present or if they recur during tapering, return to step 2 and add azathioprine (2 mg/kg/day) to treatment for 8 to 16 weeks. Continue prednisone, tapering after signs resolve.

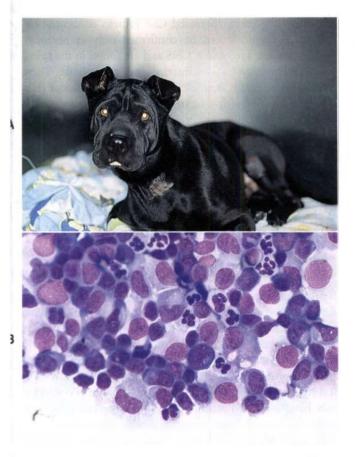
come; 2.2 mg/kg/PO q24h) to their treatment for 8 to 16 weeks. The prognosis for survival and complete resolution is excellent. Older dogs and Beagles, Bernese Mountain dogs, and German Shorthaired Pointers with breed-associated SRMA may have disease that is more difficult to control, so treatment with prednisone and azathioprine from the outset and more prolonged tapering of prednisone dose may be warranted in those dogs. Some affected Beagles develop systemic manifestations of vasculitis, thyroiditis, and amyloidosis of the spleen, liver, or kidneys.

# GRANULOMATOUS MENINGOENCEPHALITIS

GME is an idiopathic inflammatory disorder of the CNS that is believed to have an immunologic basis. GME occurs primarily in young adult dogs of small breeds, with Poodles, toy breeds, and Terriers most commonly affected. Large-breed dogs are occasionally affected. Most dogs with GME are 2 to 6 years of age, although the disease may affect older or younger dogs. Cats are not affected.

There are three distinct forms of GME. The ocular form is the least common and results in optic neuritis with an acute onset of blindness and dilated nonresponsive pupils (see Chapter 66). The focal form induces clinical signs suggestive of a single enlarging space-occupying mass with slowly progressive neurologic signs similar to a tumor. This form is most likely to affect the pontomedullary region, the forebrain, or the cervical spinal cord. The diffuse form of GME causes rapidly progressive signs of multifocal or disseminated disease affecting the brainstem, cerebrum, cerebellum, cervical spinal cord, or meninges.

Clinical signs reflect the location and nature of the lesion. Prominent features may include cervical pain, suggesting meningeal involvement, or brainstem signs such as nystagmus, head tilt, blindness, or facial and trigeminal paralysis. Ataxia, seizures, circling, and behavior change are also common. Many dogs with the diffuse form of GME have a fever and peripheral neutrophilia but no other evidence of



### FIG 69-2

**A**, A young Chinese Shar-Pei with incoordination, depression, vertical nystagmus, and a slight head tilt resulting from disseminated granulomatous meningoencephalomyelitis. **B**, Cerebrospinal fluid from this dog has increased cellularity—primarily lymphocytes, monocytes, plasma cells, and neutrophils.

systemic disease. The disseminated form of the disease has an acute to subacute progression over weeks to months, with 25% of the cases dead within 1 week. The focal form is more insidious, with progression over 3 to 6 months.

CSF analysis reveals an increase in protein concentration and a mild to marked mononuclear pleocytosis. Lymphocytes, monocytes, and occasional plasma cells predominate (Fig. 69-2). Anaplastic mononuclear cells with abundant lacy cytoplasm are sometimes present. Neutrophils are seen in two thirds of the samples, usually making up less than 20% of the cells. A single sample of CSF is sometimes normal. CSF electrophoresis typically shows evidence of blood-brain barrier disruption, and chronically affected dogs have dramatically increased intrathecal production of gamma globulins. Evaluation for infectious causes of meningoencephalomyelitis through culture and appropriate serum and CSF titers and a systemic search for neoplasia should precede a presumptive diagnosis of GME. Computed tomography (CT) or magnetic resonance imaging (MRI) usually shows a solitary contrast-enhancing mass in the brain or spinal cord with focal disease and may be normal or demonstrate patchy



### BOX 69-3

# Chemotherapy Options for Presumed Granulomatous Meningoencephalitis

### **Prednisone**

1 mg/kg PO q12h for 2 weeks, then 1 mg/kg PO q 24h for 4 weeks, then 1 mg/kg q 48h forever

### Cytosine arabinoside (Cytosar; Upjohn Pharma)

50 mg/m² body surface area SC q12h on 2 consecutive days every 21 days

### Procarbazine (Matulane, Sigma-Tau Pharmaceuticals)

25-50 mg/m² body surface area PO q 24h for 30 days, then q48h

### Cyclosporine (Neoral; Novartis)

6 mg/kg PO q12h (trough target 200-400 ng/ml)

### Leflunomide (Arava; Aventis Pharma)

4 mg/kg PO q24h, (trough target 20 µg/ml): maintenance dose of 0.5 mg/kg/day

PO, By mouth; SC, subcutaneous.

ill-defined regions of contrast enhancement with diffuse disease. Definitive diagnosis requires biopsy or necropsy for histologic examination.

Corticosteroids can occasionally halt or reverse the progression of clinical signs, particularly in animals with slowly progressive clinical signs associated with focal disease. The administration of prednisone (1 to 2 mg/kg/PO q24h) may cause a dramatic response, but clinical signs often recur quickly, with the median survival time highly variable depending on type and location of disease, ranging from longer than 12 months in dogs with focal forebrain GME to 8 days in dogs with diffuse GME. Improvement in clinical signs and survival can sometimes be seen when more aggressive chemotherapy protocols are used. Recommended drugs and protocols are outlined in Box 69-3. Radiation therapy may also greatly benefit some dogs with focal intracranial masses resulting from GME. With any protocol the best results are seen in patients with focal disease and those that receive treatment before neurologic signs are severe. Comparative efficacy between protocols is difficult to assess because of disease and patient variability and the failure to obtain a definitive pretreatment diagnosis in most patients. Most affected animals improve with treatment, but the prognosis for permanent recovery is poor.

### **NECROTIZING MENINGOENCEPHALITIS**

NME is a breed-specific idiopathic inflammatory condition affecting the brain of Pugs (pug encephalitis), Malteses, and Yorkshire Terriers (necrotizing leukoencephalitis). No infectious agent has been detected, and a genetic predisposition is likely. Necrosis and nonsuppurative necrotizing meningoencephalitis (NMG) and leptomeningitis occur, affecting

primarily the cerebral cortex in Pugs and Malteses and the cerebral cortex and brainstem in Yorkshire Terriers. Affected dogs first show clinical signs between 9 months and 7 years of age.

Dogs with rapidly progressive cerebral cortical disease caused by NME are presented with seizures and neurologic signs referable to the cerebrum and meninges. They may have difficulty walking or may be weak or lack coordination. Circling, head pressing, cortical blindness, and neck pain are common. Affected Yorkshire Terriers may have a head tilt and cranial nerve abnormalities. Neurologic deterioration is rapid, and within 5 to 7 days the dogs develop uncontrollable seizures or become recumbent, unable to walk, and comatose.

Dogs with a more slowly progressive form of NME are also commonly presented with a generalized or partial motor seizure, but these dogs are neurologically normal after the seizure. Seizures then recur at varying intervals from a few days to a few weeks, followed by the development of other neurologic signs referable to the cerebral cortex. Survival times are generally only a few weeks, with a maximum survival time of less than 6 months from the time of initial presentation.

A diagnosis of NME should be suspected on the basis of signalment and characteristic clinical and clinicopathologic features. Hematologic and serum biochemistry findings are unremarkable. Imaging studies are consistently abnormal, with focal hypodense areas within the brain parenchyma visible on CT and areas of high signal intensity seen on MRI. CSF analysis reveals a high protein concentration and an increased nucleated cell count, with the predominant cell type being the small lymphocyte. Definitive diagnosis requires autopsy or brain biopsy.

No specific treatment exists for this disease. Treatment with antiepileptic doses of phenobarbital may decrease the severity and frequency of the seizures for a short period of time. Corticosteroids are commonly administered (as for GME) but do not appear to alter the course of this disease. There are some anecdotal reports of improvement after the administration of mycophenolate mofetil (20 mg/kg, administered orally q12h for 30 days, then 10 mg/kg q12h for the remainder of the animal's life), but the prognosis for improvement and survival must be considered poor.

# FELINE POLIOENCEPHALOMYELITIS

A nonsuppurative encephalomyelitis with no etiologic agent identified occasionally causes progressive seizures or spinal cord signs in young adult cats. Affected cats range from 3 months to 6 years of age, with most cats being younger than 2 years old. Affected animals have a subacute to chronic progressive course of neurologic signs. Pelvic limb hyporeflexia may accompany ataxia and paresis of the pelvic limbs, and intention tremors of the head and seizures may occur. Seizures and behavior change may be the only signs observed in some cats.

Clinicopathologic findings are normal in most cats. CSF analysis reveals a mild increase in CSF mononuclear cells and

a normal or slightly increased CSF protein concentration. Definitive diagnosis can be confirmed only at necropsy. Lesions are confined to the CNS and are found in the spinal cord, cerebral cortex, brainstem, and cerebellum. These lesions include perivascular cuffing with mononuclear cells, lymphocytic meningitis, neuronophagia, and the formation of glial nodules. White matter degeneration and demyelination are also present. The prognosis is poor, although reports exist of spontaneous recovery from a clinically similar disorder in a few cats.

# INFECTIOUS INFLAMMATORY DISORDERS

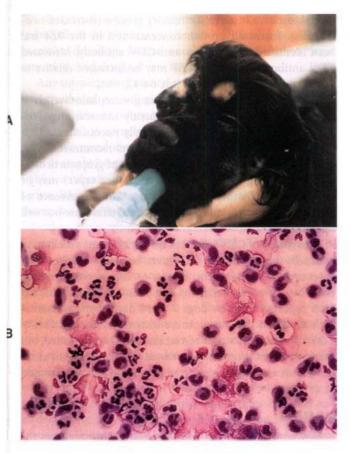
# FELINE IMMUNODEFICIENCY VIRUS ENCEPHALOPATHY

Neurologic abnormalities associated with feline immunodeficiency virus (FIV) encephalopathy in cats include behavioral and mood changes, depression, persistent staring, inappropriate elimination, seizures, twitching of the face and tongue, and occasionally paresis. A presumptive diagnosis of FIV encephalopathy is made on the basis of suggestive clinical signs and positive FIV serology, but because FIV-infected cats have increased susceptibility to numerous neoplastic and infectious causes of encephalitis, it is important to carefully exclude other neurologic diseases. CSF analysis reveals an increase in lymphocytes and normal or only slightly increased CSF protein concentration. FIV antibodies can be demonstrated in the CSF of most affected cats. Care must be taken to keep from contaminating the CSF with blood during collection because serum antibody titers are higher than those in the CSF. Culture of freshly collected CSF may yield the virus. Zidovudine (AZT: 5 mg/kg, administered orally q12h) administration may reduce the severity of neurologic impairment in some cats.

# BACTERIAL MENINGOENCEPHALOMYELITIS

Bacterial infection of the CNS is uncommon in dogs and cats. It may result from direct extension of infection from an extraneural site such as the middle ear, eye, sinus, or nose or because of a penetrating injury to the skull. Hematogenous dissemination from extracranial foci occurs rarely, except in neonates with omphalophlebitis and dogs and cats with severe immunodeficiency. In contrast to people, bacterial meningitis and meningoencephalomyelitis in dogs and cats is not caused by microorganisms having a specific predilection for the nervous system. Bacterial infections of the CNS are instead associated with the wide variety of organisms infecting primary sites.

Clinical signs of bacterial infection of the CNS commonly include pyrexia, neck pain, vomiting, and bradycardia. Neurologic abnormalities reflect the location of damaged parenchyma and may include seizures, coma, blindness, nystagmus, head tilt, paresis, or paralysis. The clinical course is usually rapidly progressive and frequently fatal. Affected animals are



A, A 4-year-old Cocker Spaniel with a chronic retrobulbar abscess developed fever and severe depression.

B, Cerebrospinal fluid from this dog reveals septic inflammation. Postmortem examination confirmed communication between the retrobulbar abscess and the central nervous system.

almost always systemically ill. Shock, hypotension, and disseminated intravascular coagulation are common. Routine laboratory tests often reflect the underlying inflamatory process.

CSF analysis reveals increased protein concentration and a predominantly neutrophilic pleocytosis, with cell counts often >500 cells/ul. Neutrophils in the CSF may appear degenerate, and occasionally intracellular bacteria are seen (Fig. 69-3). Treatment with antibiotics before CSF is collected may lower the CSF cell count and result in a predominance of mononuclear cells. The rate of organism recovery is improved by inoculation of CSF into broth enrichment media, but fewer than 50% will have positive CSF cultures. Whenever bacterial meningitis is suspected, diagnostic evaluation should include CSF cytologic analysis; CSF anaerobic and aerobic bacterial culture; blood and urine bacterial cultures; ophthalmologic and otic examination; screening radiographs of the spine, skull, and thorax; and abdominal ultrasound examination. MRI can be used to identify defects in the skull or infections or tumors extending into the cranial vault from the ear, eye, sinus, or nose. The presence of systemic bacterial illness or the identification of an extraneural focus of infection in a dog or cat with inflammatory CSF should prompt immediate treatment for suspected bacterial infection of the CNS. If the focus of underlying infection can be determined, that site should be cultured. Therapy usually is initiated before culture results are available.

Bacterial meningitis is a life-threatening infection and requires rapid and aggressive treatment. Appropriate therapy of CNS infections is based on identification of the causative organism and selection of an appropriate antimicrobial agent that will reach high concentrations in the CSF and CNS tissues. Enrofloxacin and third-generation cephalosporins (e.g., ceftriaxone, cefotaxime) are good choices for gram-negative infections, and metronidazole can be used for anaerobic infections. While inflammation persists, ampicillin and amoxicillin with clavulonic acid are also effective and may be the best choice for gram-positive infections. Initial treatment with a combination of ampicillin (22 mg/kg, administered intravenously q6h), cefotoxime (20-40 mg/kg, administered intravenously q6h), and metronidazole (15 mg/ kg administered once intravenously, then 7.5 mg/kg intravenously q8h or 10-15 mg/kg orally q8h) may be warranted if the infectious agent is unknown. Whenever possible, antibiotics should be administered intravenously for 3 to 5 days to achieve high CSF concentrations, and oral therapy should be continued for 4 weeks after recovery. Concurrent intravenous fluids and systemic support are important, and anticonvulsants should be administered to patients having seizures (see the discussion of status epilepticus in Chapter 67). Antiinflammatory drugs or corticosteroids (dexamethasone, 0.2 mg/kg IV q12h) are sometimes administered for the first 2 days of antibiotic treatment to minimize the inflammatory consequences of antibiotic-induced bacterial lysis.

The response to antibiotic therapy is variable, and relapses are common. The prognosis should be considered guarded because even with appropriate therapy many animals die. However, treatment should be attempted because some individual patients respond dramatically to therapy and have complete resolution of their neurologic defects.

#### **CANINE DISTEMPER VIRUS**

Canine distemper virus (CDV) is a paramyxovirus that commonly affects the CNS of dogs. Widespread vaccination has substantially decreased the incidence of clinically apparent CDV infections in many regions, but outbreaks still occur among unvaccinated dogs and sporadically in vaccinated dogs. Clinical signs vary, depending on virulence of the virus strain, environmental conditions, and host age and immune status. Most CDV infections are probably subclinical or are associated with mild signs of upper respiratory tract infection that resolve without therapy. Young, immunocompromised, and unvaccinated dogs are most likely to develop severe generalized distemper.

Progressive generalized infection with CDV most commonly affects unvaccinated puppies between 12 and 16 weeks of age. The first sign of infection is a mild serous to

mucopurulent ocular and nasal discharge followed by a dry cough and sometimes tonsillitis. The cough becomes moist and productive as pneumonia develops. Affected dogs are depressed, inappetent, and often febrile. Diarrhea develops and may be mild or severe. Hyperkeratosis of the footpads and nose may occur. Neurologic signs begin 1 to 3 weeks after dogs start to recover from systemic illness and may include dementia, disorientation, seizures, cerebellar or vestibular signs, tetraparesis, and ataxia. Neck pain is uncommon. Seizures can be of any type, depending on the region of the brain affected, but "chewing gum" seizures caused by polioencephalomalacia of the temporal lobes are commonly described. Myoclonus, a repetitive rhythmic contraction of a group of muscles resulting in repetitive flexion of a limb or contractions of the muscles of mastication, is often referred to as distemper chorea and is very common in dogs with distemper encephalomyelitis. Anterior uveitis, optic neuritis, or chorioretinitis occurs in some infected dogs. Dogs surviving mild CDV infection before eruption of their permanent teeth will often have irregular dental surfaces and brown discoloration of their teeth subsequent to virusinduced enamel hypoplasia. Older animals occasionally develop chronic encephalomyelitis months to years after prior CDV infection and recovery (old dog encephalitis), with neurologic abnormalities that include progressive tetraparesis or vestibular dysfunction in the absence of systemic signs.

CDV is diagnosed on the basis of history, physical examination, and laboratory findings. In many animals a history of mild to severe gastrointestinal and respiratory illness precedes the onset of neurologic signs. Results of a CBC may be normal or may reveal a persistent lymphopenia; distemper inclusions can sometimes be found in the circulating lymphocytes and erythrocytes. Optic neuritis, chorioretinitis, and retinal detachment may be detected during an ophthalmologic examination. Irregular, ill-defined, gray-to-pink densities in the tapetal or nontapetal region suggest acute or active choriorctinitis, whereas well-defined hyperreflective regions are more indicative of chronic infection with scarring.

Early in an infection, immunofluorescent techniques, using anti-CDV antibodies, may reveal CDV in cytologic smears prepared from conjunctival, tonsilar, or nasal epithelium. Virus may be detected past these initial stages in epithelial cells and macrophages obtained from the lower respiratory tract by tracheal wash. The virus persists for up to 60 days in the skin, footpads, and CNS; thus immunohistochemical techniques can be applied to biopsy or necropsy specimens for diagnosis. Biopsy of the haired skin of the dorsal neck can be used for antemortem immunohistochemical testing to confirm acute and subacute infection with CDV. Reverse-transcriptase polymerase chain reaction (RT-PCR) can also be used to detect CDV RNA in whole blood, buffy coat preparations, CSF, and tissues of affected dogs.

Distemper meningoencephalitis characteristically causes an increase in protein concentration and a mild lymphocytic pleocytosis in the CSF; occasionally, the CSF is normal or more indicative of an inflammatory process (increased neutrophils). Increased protein concentration in the CSF has been identified primarily as anti-CDV antibody. Measured CDV antibody titer in the CSF may be increased relative to the serum titer (C-value, see Box 64-4).

Treatment of acute CDV meningoencephalomyelitis is supportive, nonspecific, and frequently unrewarding. Progressive neurologic dysfunction usually necessitates euthanasia. Anticonvulsant therapy has been recommended to control seizures. Antiinflammatory doses of glucocorticosteroids (0.5 mg/kg q12h PO for 10 days, then taper) may be used to control other neurologic signs in the absence of systemic disease; however, their beneficial effects are not well documented.

Prevention of CDV infection through routine vaccination is usually very effective. CDV can, however, develop with exposure following stress, illness, or immunosuppression, even in a currently vaccinated dog. Meningoencephalitis has been reported in a few dogs 7 to 14 days after vaccination with modified live virus-canine distemper vaccines (MLV-CDV). Particular batches of vaccines may be implicated, but vaccination of immunosuppressed neonates, particularly those with a known or suspected parvoviral infection, should be avoided.

#### RABIES

Rabies virus infection in dogs and cats is almost always the result of a bite from an infected animal that has rabies virus in its saliva. Most dogs and cats are infected through contact with wildlife vectors (e.g., skunks, raccoons, foxes, bats). Although the prevalence of wildlife rabies has been increasing, cases of rabies in pet dogs and cats have been decreasing as a result of routine vaccination protocols. The incubation period from the time of the bite to the onset of clinical signs is extremely variable (1 week to 8 months), with average incubation 3 to 8 weeks. Once neurologic signs develop, the disease is rapidly progressive, with death occurring within 7 days in most animals.

Rabies can have a wide range of clinical signs, which makes it difficult to differentiate from other acute, progressive encephalomyelitis syndromes. Because of its public health significance, rabies should be on the list of differential diagnoses considered in every animal with rapidly progressing neurologic dysfunction and precautions should be taken to minimize human exposure. Rabies infection has classically been divided into two major types: furious and paralytic. Dogs and cats typically undergo an early prodromal phase lasting 2 to 3 days during which they may be apprehensive or nervous and may lick or chew at the site of inoculation. This can be followed by a furious or psychotic phase (1 to 7 days) in which animals are increasingly irritable and excitable, often snapping at imaginary objects and biting at their cage or surroundings. They become incoordinated and may exhibit generalized seizures, progressing to death. Animals with the paralytic or dumb type of rabies develop generalized LMN paralysis progressing from the site of inoculation to involve the entire CNS within a few (range 1 to 10) days. Cranial nerve paralysis may be the first sign seen (especially if the bite was on the face). Difficulty swallowing, excessive drooling, hoarse vocalization, diminished facial sensation, and dropped jaw may be seen.

Any unvaccinated animal with an acute, rapidly progressive course of neurologic disease should be suspected of having rabies. Ancillary testing should be performed with caution, minimizing exposure of personnel. CSF analysis reveals increased mononuclear cells and protein concentration, as might be expected with any viral encephalomyelitis. Rabies antibody may be increased in CSF compared with serum. Biopsies obtained from the dorsal skin at the nape of the neck or the maxillary sensory vibrissae may be positive for rabies virus antigen; however, although positive results are reliable, negative results are not. Definitive diagnosis of rabies encephalitis is through the demonstration of rabies virus antigen by immunohistochemical techniques in the brain tissue (thalamus, pons, and medulla) of an infected animal postmortem. Because of the risk associated with inadvertent human exposure, it is recommended that all unvaccinated animals with progressive neurologic dysfunction of unknown origin undergo postmortem evaluation for rabies.

Fortunately, vaccinations have been extremely effective in reducing the prevalence of rabies in pet dogs and cats and in decreasing the incidence of rabies infection in humans. Inactivated products and recombinant vaccines are available and are relatively safe and effective when used as directed. Dogs and cats should receive their first rabies vaccine after 12 weeks of age and then again at 1 year of age. Subsequent boosters are administered every 1 to 3 years, depending on the vaccine used and local public health regulations. Rarely, soft tissue sarcomas have developed in cats at the site of rabies virus prophylactic inoculation. Postvaccinal polyradiculoneuritis causing an ascending LMN tetraparesis has also been reported occasionally in dogs and

#### **FELINE INFECTIOUS PERITONITIS**

Progressive neurologic involvement is common in cats affected with the dry form of feline infectious peritonitis (FIP). Neurologic signs may include seizures, cerebellar signs, vestibular dysfunction, and paresis. Most affected cats have a fever and systemic signs such as anorexia and weight loss. Concurrent anterior uveitis, iritis, keratic precipitates, and chorioretinitis are common and should raise the suspicion of this disease. Careful abdominal palpation will occasionally reveal organ distortion caused by concurrent granulomas in the abdominal viscera.

Typically, the complete blood count is inflammatory and serum globulin concentrations may be very high. Serum tests for anticoronavirus antibodies are variable. MRI and CT may reveal multifocal granulomatous lesions and secondary hydrocephalus or may be normal. Typical findings on CSF analysis include a marked neutrophilic or pyogranulomatous pleocytosis (>100 cells/µl; >70% neutrophils) and an increase in CSF protein concentration (>200 mg/dl). In a few

cases, however, CSF will be normal or only slightly inflammatory. Coronavirus antibody will usually be positive in the CSF, and coronavirus can sometimes be detected in the CSF and affected tissue using RT-PCR. The prognosis for cats with CNS FIP is very poor. Some palliation may be achieved with immunosuppressive and antiinflammatory medications (see Chapter 97 for more information on FIP).

#### **TOXOPLASMOSIS**

Toxoplasma gondii infections can be acquired transplacentally, through ingestion of tissues containing encysted organisms, or through ingestion of food or water contaminated by cat feces containing oocysts. Most infections are asymptomatic. Transplacentally infected kittens may develop acute fulminating signs of liver, lung, CNS, and ocular involvement. Disease in older animals results from reactivation of a chronic encysted infection. Infection is evident in the lung, CNS, muscle, liver, pancreas, heart, and eye in cats. In dogs lung, CNS, and muscle infections predominate.

CNS toxoplasmosis can cause a variety of signs, including behavioral change, seizures, circling, tremors, ataxia, paresis, and paralysis. Muscle pain and weakness caused by *Toxoplasma* myositis is discussed in Chapter 72.

Routine labwork may be normal in dogs and cats with CNS toxoplasmosis, or a neutrophilic leukocytosis and eosinophilia may be seen. Serum globulins may be increased. Liver enzymes are increased when there is hepatic infection, and creatine kinase (CK) is increased in animals with myositis. Cats commonly have concurrent uveitis or chorioretinitis. CSF analysis typically reveals increased protein concentration and a mild to moderately increased nucleated cell count. Lymphocytes and monocytes usually predominate, but occasionally the pleocytosis is neutrophilic or eosinophilic. The CSF concentration of antibody directed against T. gondii may be increased relative to serum concentration, suggesting local production of specific antibody and an active infection. Rarely, cytologic examination of the CSF reveals T. gondii organisms within host cells, allowing a definitive diagnosis of toxoplasmosis.

Antemortem diagnosis of CNS toxoplasmosis may be difficult. If other organ systems are involved, finding organisms in samples from affected extraneural tissues allows definitive diagnosis. A fourfold rise in IgG titer in two serum samples taken 3 weeks apart or a single elevated IgM titer in a patient with neurologic signs supports a diagnosis of toxoplasmosis, but antibody titers are negative in some animals with severe disease (see Chapter 99). CSF titers should be interpreted in conjunction with evidence for blood-brain barrier disruption, calculating the antibody coefficient or c-value (see Box 64-4). PCR can sometimes be used to identify *Toxoplasma* in blood, aqueous humor, CSF, muscle, or nervous system tissue from affected dogs and cats.

Recommended treatment for meningoencephalomyelitis caused by toxoplasmosis in dogs and cats consists of clindamycin hydrochloride (10 mg/kg PO q8h for at least 4 weeks). This drug has been shown to cross the blood-brain barrier and has been used with success in a limited number of

animals. Trimethoprim-sulfadiazine (15 mg/kg, administered orally q12h) can be used as an alternate anti-Toxoplasma drug, especially in combination with pyrimethamine (1 mg/ kg/day), but if this is used for long-term treatment, folic acid supplementation should be considered. The prognosis for recovery is grave in animals with profound neurologic dysfunction. Affected cats should be routinely tested for concurrent feline leukemia virus (FeLV) and FIV infections. Neurologic, ocular, and muscular manifestations of toxoplasmosis are not usually associated with patent infection and oocyte shedding in cats, so isolation of affected animals is not necessary.

#### **NEOSPOROSIS**

Neospora caninum is a protozoan parasite that causes neuromuscular disease in dogs. Domestic dogs and coyotes are definitive hosts, shedding oocysts in their stool after ingestion of N. caninum cysts in muscle from intermediate hosts (primarily deer and cattle). The predominant route of transmission is transplacental, causing acute symptomatic infection in some puppies and subclinical infection leading to encystment in neural and muscle tissues in others. Young puppies 6 weeks to 6 months of age typically develop weakness, loss of patellar reflexes, and finally LMN paralysis of the rear limbs as a result of inflammation of the muscles and nerve roots (Fig. 69-4). Multiple puppies from a litter may be affected. If treatment is not initiated promptly, severe atrophy and contracture of affected muscles fixes the rear limbs in rigid extension (Fig. 69-5). Most affected puppies are bright and alert and otherwise normal. Disease in older animals usually results from reactivation of a chronic encysted infection acquired congenitally or through ingestion of tissue cysts. These dogs commonly have signs of multifocal CNS involvement. Paraparesis, tetraparesis, cerebellar signs, seizures, and cranial nerve abnormalities are reported. Some dogs have concurrent myositis. Rarely, a rapidly progressive diffuse LMN paralysis similar to acute



A 10-week-old Irish Wolfhound puppy with a crouched rear limb stance, quadriceps muscle weakness, and atrophy and patellar areflexia caused by Neospora caninum myositis and lumbar radiculoneuritis. This dog recovered after clindamycin treatment.

idiopathic polyradiculoneuritis has been reported. Most affected dogs are systemically normal, but occasionally systemic neosporosis will occur, causing fever, pneumonia, hepatitis, pancreatitis, esophagitis, or pyogranulomatous dermatitis.

Hematologic and biochemical findings vary and depend on the organ systems involved. With muscle disease, serum CK and aspartate aminotransferase (AST) activities are increased. Serology can be used to support the diagnosis, but there is no correlation between serum titer and severity of clinical signs. Puppies may have maternally derived antibodies without being infected; however, these should be gone by day 32 of life. CSF may be normal or may have mild increases in protein concentration (20 to 150 mg/dl) and leukocyte count (10 to 100 cells/ 1), with monocytes and lymphocytes predominating; some neutrophils and eosinophils may be present. Specific antibodies may occasionally be detected in the CSF. Immunocytochemical staining can be used to identify Neospora and differentiate it from Toxoplasma in muscle biopsies antemortem and in muscle and CNS tissues postmortem. Treatment with clindamycin hydrochloride (10 mg/ kg PO q8h for at least 4 weeks) is most effective in dogs without severe neurologic signs. Multifocal signs, rapid progression of signs, pelvic limb rigid hyperextension, and delayed treatment are all associated with a poor prognosis for recovery.

#### LYME DISEASE

Lyme neuroborreliosis, resulting from infection of the CNS by the spirochete Borrelia burgdorferi, has been well documented in people, but there are few reports of dogs with neurologic signs convincingly caused by Lyme disease. Most affected dogs have concurrent polyarthritis, lymphadenopathy, and fever. Reported signs of neurologic system involvement include aggression, other behavior changes, and seizures. CSF may be normal or only slightly inflammatory, and there may be an increase in anti-B. burgdorferi antibody in the CSF compared with serum. Although it is rare, Lyme



FIG 69-5 A young Labrador Retriever with rigid extension of the rear limbs caused by pediatric neosporosis.

neuroborreliosis should be considered in the differential diagnosis of disease involving the CNS in dogs from endemic regions. Early antibiotic treatment may be effective, but it is important to select an effective antibiotic that is capable of reaching high concentrations in the CSF. Ceftriaxone (25 mg/ kg, administered intravenously or subcutaneously q24h for 14-30 days), doxycycline (10 mg/kg, administered orally q12h for 30 days), and amoxicillin (20 mg/kg, administered orally 98h for 30 days) have all been recommended.

## MYCOTIC INFECTIONS

Disseminated systemic mycotic infections may occasionally involve the CNS and eyes. Clinical signs depend on the fungus involved and include gastrointestinal, respiratory, or skeletal problems in conjunction with neurologic and ocular signs. The most common neurologic signs are depressed mentation, behavior change, seizures, circling, and paresis. Ocular examination may reveal uveitis, chorioretinitis, retinal detachment, or optic neuritis. Typical abnormalities on CSF analysis include a neutrophilic pleocytosis and increased protein content. Diagnosis is usually by finding the organism in extraneural infected tissues. Therapy may be attempted; however, the prognosis is poor when the nervous system is involved.

It is uncommon for systemic mycoses to present with only neurologic signs. The exception is infection caused by the encapsulated yeasts Cryptococcus neoformans and Cryptococcus gatti. These organisms have a predilection for the CNS in the dog and cat. Infection occurs via extension from the nose through the cribiform plate and via hematogenous dissemination of severe disease in the dog or cat.

In cases of cryptococcal meningoencephalitis, CSF analysis reveals increased protein concentration and cell counts. A neutrophilic pleocytosis is most common, but eosinophils have been reported. Organisms can be visualized in the CSF in approximately 60% of cases. Fungal culture of the CSF should be considered in dogs with inflammatory CSF in which no organisms are visible. Detection of capsular antigen in the CSF or serum of affected animals using a latex agglutination test may also be a useful aid to diagnosis. Cytologic examination of nasal exudate, draining tracts, enlarged lymph nodes, and granulomas located extraneurally may yield the diagnosis. The organism is readily visible using Gram's stain, India ink, or Wright's stain. Treatment of CNS cryptococcus is usually attempted using amphotericin B or fluconazole, both of which penetrate the CNS. Itraconazole is sometimes effective (see Chapter 98 for more information).

#### RICKETTSIAL DISEASES

Rocky Mountain spotted fever (RMSF), caused by Rickettsia rickettsii, and ehrlichiosis, caused by Ehrlichia canis, commonly involve the CNS of dogs, causing meningoencephalomyelitis. Neurologic signs are seen in approximately 30% of dogs with both diseases, but the signs are most severe in dogs with RMSF. Neurologic abnormalities in dogs with RMSF tend to be more acute and progressive than those seen

with ehrlichiosis. Neurologic signs with either disease include neck pain, mental changes, ataxia, vestibular signs, stupor, and seizures. Neurologic abnormalities have not been recognized in dogs without concurrent systemic disease. Signs of systemic disease depend on the degree of involvement of other organ systems but may include fever, anorexia, depression, vomiting, oculonasal discharge, cough, dyspnea, and lymphadenopathy. Hematologic abnormalities including anemia, thrombocytopenia, leukocytosis, and hyperglobulinemia are common and should prompt consideration of tick-borne illness in dogs from endemic regions with neurologic signs. The organisms of granulocytic ehrlichiosis (Ehrlichia ewingii and Anaplasma phagocytophilia) also cause thrombocytopenia, polyarthritis, and meningitis in dogs.

Although the number of cases reported is small, neutrophils seem to predominate in the CSF of dogs with RMSF, whereas lymphocytes or neutrophils predominate in ehrlichiosis; the CSF is normal in some dogs with each disease. In some dogs with granulocytic ehrlichiosis, neutrophils in the blood or in the CSF may contain morulae. Serologic testing or PCR (blood or CSF) is essential to confirm the diagnosis of rickettsial infection and to differentiate between these diseases. Treatment with doxycycline (5 to 10 mg/kg, administered orally or intravenously q12h) is effective in most cases. Short-term treatment with corticosteroids may also be warranted. Dramatic clinical improvement should be expected within 24 to 48 hours of initiating treatment. The presence of neurologic signs may slow recovery, and in some cases the neurologic damage is irreversible (see Chapter 96 for more information on rickettsial diseases).

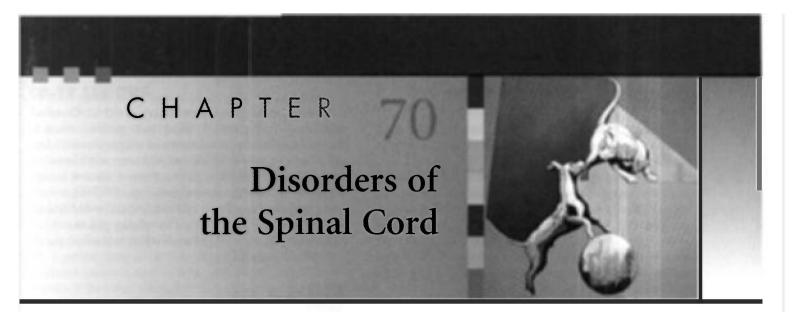
# PARASITIC MENINGITIS, MYELITIS, AND ENCEPHALITIS

Meningitis and meningoencephalitis caused by aberrant parasite migration have been reported in the dog and cat. In these diseases migration and growth of parasites can result in extensive damage to the neural parenchyma. An eosinophilic CSF pleocytosis should prompt consideration of parasitic migration through the CNS, although several more common neurologic disorders should also be considered, including intracranial neoplasia, toxoplasmosis, neosporosis, and GME. An apparently immune-mediated eosinophilic meningitis has also been described in young dogs, particularly Golden Retrievers. Diagnostic evaluation of animals with eosinophilic CSF should include a fundic examination, complete blood count, serum biochemistry profile, urinalysis, serum and CSF titers for Toxoplasma and Neospora, thoracic and abdominal radiographs, abdominal ultrasound, fecal flotation, and heartworm antigen testing. CT and MRI may document necrosis along the path of parasite migration within the CNS. Definitive diagnosis of parasitic CNS disease requires pathologic demonstration of the parasite in the CNS. Empirical treatment with ivermectin should be considered if parasite migration is likely (200 to 300 µg/kg, administered orally or subcutaneously every 2 weeks for three treatments). Antiinflammatory treatment with prednisone may also be indicated.

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# CHAPTER OUTLINE

GENERAL CONSIDERATIONS LOCALIZING SPINAL CORD LESIONS

C1-C5 Lesions

C6-T2 Lesions

T3-L3 Lesions

L4-S3 Lesions

Diagnostic Approach ACUTE SPINAL CORD DYSFUNCTION

Trauma

Hemorrhage/Infarction

Acute Intervertebral Disk Disease

Fibrocartilaginous Embolism

Atlantoaxial Instability

Neoplasia

PROGRESSIVE SPINAL CORD DYSFUNCTION

**Subacute Progressive Disorders** 

Chronic Progressive Disorders

Progressive Disorders in Young Animals

Nonprogressive Disorders in Young Animals

# **GENERAL CONSIDERATIONS**

Spinal cord disorders can be caused by anomalies, degeneration, neoplasia, inflammatory conditions, external trauma, internal trauma from disk extrusion, hemorrhage, or infarction (Box 70-1). Clinical signs depend on lesion location and severity and frequently include focal or generalized pain, paresis, paralysis, and occasionally an inability to urinate. Examination of the signalment, history, onset, and progression of the disease can provide valuable information necessary for establishing a likely cause. Congenital malformations are present at birth, do not progress, and are often breed-associated. External trauma, type 1 intervertebral disk extrusion, and vascular disorders (hemorrhage or infarction) are usually associated with acute, nonprogressive

signs. Infectious or noninfectious inflammatory disorders typically have a subacute and progressive course, whereas tumors and degenerative processes are most often slowly progressive.



BOX 70-1

#### Common Causes of Spinal Cord Dysfunction

#### Acute (Minutes to Hours)

External trauma

Hemorrhage/vascular infarction

Type 1 intervertebral disk extrusion

Fibrocartilagenous embolism

Atlantoaxial subluxation

#### Subacute Progressive (Days to Weeks)

Infectious diseases

Noninfectious inflammatory disease

Rapidly growing tumors (lymphoma, metastatic neoplasia)

Diskospondylitis

#### **Chronic Progressive (Months)**

Neoplasia

Intraspinal articular cysts

Arachnoid cysts

Type 2 intervertebral disk protrusion

Degenerative myelopathy

Cauda equina syndrome

Cervical spondylomyelopathy

#### **Progressive in Young Animals**

Neuronal abiotrophies and degenerations

Metabolic storage diseases

Atlantoaxial instability

#### Congenital (Constant)

Spina bifida

Caudal dysgenesis of Manx cats

Spinal dysraphism

Syringomyelia/hydromyelia

# LOCALIZING SPINAL CORD LESIONS

Once a complete neurologic examination has been performed and postural reactions, proprioception, strength, muscle tone, and spinal reflexes have all been assessed, it is possible to identify the location of a spinal cord lesion. Functionally, the spinal cord can be divided into four regions: the cranial cervical spinal cord (C1-C5), the cervical intumescence (C6-T2), the thoracolumbar region (T3-L3), and the lumbar intumescence (L4-S3). Signs allowing localization of spinal cord lesion to each site and differential diagnoses considered for disease localizing to each site are listed in Table 70-1 and Box 70-2.

#### C1-C5 LESIONS

Lesions of the cranial cervical spinal cord cause upper motor neuron (UMN) paresis in all four limbs. Because the spinal cord pathways to the rear limbs are more superficial in the cord than those to the forelimbs, rear limb deficits are usually worse than forelimb deficits in patients with mild compressive C1-C5 spinal cord lesions. Central canal lesions (e.g., intramedullary neoplasia, infarcts, hydromyelia) in the C1-C5 region occasionally cause severe UMN deficits in the forelimbs with nearly normal rear limbs (central cord

syndrome) as the superficially located white matter tracts to the rear limbs are spared. Most lesions of the C1-C5 spinal cord cause a long-strided, ataxic gait; postural reaction deficits, including decreased conscious proprioception (slow knuckling); increased extensor muscle tone; and normal to increased spinal reflexes in all four limbs. Unilateral lesions of the cervical cord cause hemiparesis and UMN signs only in the ipsilateral rear limbs and forelimbs. Cervical lesions are rarely severe enough to cause loss of deep pain sensation; such a severe injury would cause complete respiratory paralysis and rapid death.



TABLE 70-1

Neurologic Findings in Dogs and Cats with Spinal Cord Lesions

THORACIC LIMBS	PELVIC LIMBS
UMN	UMN
LMN	UMN
Normal	UMN
Normal	LMN
	UMN LMN Normal

UMN, Upper motor neuron signs; LMN, lower motor neuron signs.



BOX 70-2

# Disorders Affecting Each Spinal Cord Region

#### C1-C5

Intervertebral disk disease Fibrocartilagenous embolism

Hemorrhage Fracture/luxation

Diskospondylitis

Meningomyelitis, infectious

Granulomatous meningoencephalomyelitis

Neoplasia

Arachnoid cyst

Spinal articular cyst

Cervicospondylomyelopathy

Syringohydromyelia

Atlantoaxial subluxation

Steroid responsive meningitis-arteritis

#### C6-T2

Intervertebral disk disease

Fibrocartilagenous embolism

Hemorrhage

Fracture/luxation

Diskospondylitis

Meningomyelitis, infectious

Granulomatous meningoencephalomyelitis

Neoplasia

Arachnoid cyst

Spinal articular cyst

Cervicospondylomyelopathy

Brachial plexus avulsion

#### T3-L3

Intervertebral disk disease

Fibrocartilagenous embolism

Hemorrhage

Fracture/luxation

Diskospondylitis

Meningomyelitis, infectious

Granulomatous meningoencephalomyelitis

Neoplasia

Arachnoid cyst

Spinal articular cyst

Degenerative myelopathy

#### L4-S3

Intervertebral disk disease

Fibrocartilagenous embolism

Hemorrhage

Fracture/luxation

Diskospondylitis

Meningomyelitis, infectious

Granulomatous meningoencephalomyelitis

Neoplasia

Cauda equina syndrome

Spina bifida

Sacrocaudal dysgenesis

#### **C6-T2 LESIONS**

Lesions of the spinal cord between C6 and T2 result in paresis of all four limbs and ataxia that is most pronounced in the rear limbs. The spinal cord segments containing the cell bodies of the nerves of the brachial plexus are affected in this region, so lower motor neuron (LMN) signs of weakness, a short-strided "choppy" gait, muscle atrophy, and hyporeflexia predominate in the forelimbs. Disruption of ascending and descending spinal cord tracts in this region causes UMN deficits in the rear limbs, including ataxia, a long stride, loss of conscious proprioception, delayed postural reactions, increased extensor muscle tone, and normal to increased reflexes. If the lesion affects only the central cord, sparing the superficially located long tracts to the rear limbs, the forelimb LMN signs may be much more pronounced than the rear limb UMN signs. When C6-T2 lesions are unilateral, ipsilateral forelimbs and rear limbs will be affected. Horner's syndrome may be seen if the T1-T2 spinal cord segments or nerve roots are involved (see Chapter 66), and the ipsilateral cutaneous trunci reflex may be lost if the C8-T1 spinal cord segments or nerve roots are damaged. Because the phrenic nerve originates at C5 to C7, a severe lesion in this region could also cause diaphragmatic paralysis.

#### **T3-L3 LESIONS**

Lesions of the spinal cord between T3 and L3 cause UMN paresis and ataxia affecting the rear limbs (see Table 70-1), with normal forelimbs. Examination of the rear limbs reveals a long, incoordinated stride; loss of conscious proprioception; delayed postural reactions; increased extensor muscle tone; and normal to increased reflexes. As compressive lesions of the spinal cord in this region become more severe,

there is a predictable worsening of the neurologic deficits (Fig. 70-1). With severe focal lesions in this region there may be a loss of the cutaneous trunci reflex caudal to the site of the lesion.

#### **L4-S3 LESIONS**

Lesions affecting the lumbar intumescence cause LMN signs in the rear limbs. Severe weakness, muscle atrophy, and loss of reflexes are apparent in the rear limbs, and forelimbs are normal. Animals that can still walk exhibit a short-strided rear limb gait. Bladder dysfunction and paresis or paralysis of the anal sphincter and tail are common with severe lesions. Lesions that compress the lumbar, sacral, and caudal nerve roots as they extend caudally from the end of the spinal cord within the vertebral canal (the cauda equina) usually cause pain at the site and, when severe, cause LMN dysfunction as well.

## **DIAGNOSTIC APPROACH**

Lesions should be localized to a spinal cord region on the basis of the neurologic examination. It is important to recognize that spinal cord segments do not correlate directly with vertebral location in the dog and cat (Table 70-2; Fig. 70-2). The C6-T2 spinal cord segments of the cervical intumescence are located within vertebrae C4-T2. The L4-S3 spinal cord segments of the lumbar intumescence are located within vertebrae L3-L5 in dogs and L3-L6 in cats. The spinal cord is shorter than the vertebral canal, with the caudal segments ending at approximately the L6 vertebra in dogs and the L7 vertebra in cats. The nerve roots arising from the L7, sacral, and caudal spinal cord segments (the caudal equina) course caudally within the vertebral canal to their

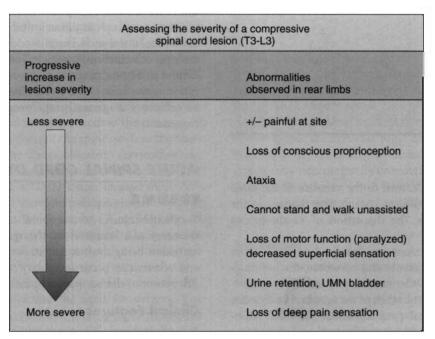
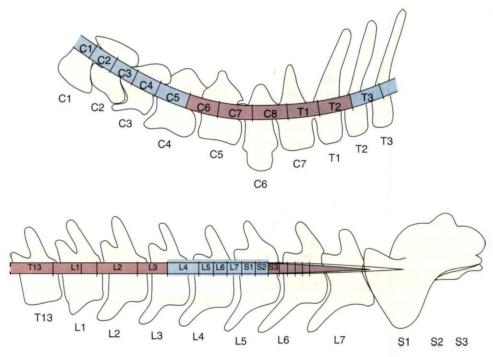


FIG 70-1
Assessing the severity of a compressive lesion of the T3-L3 spinal cord.



**FIG 70-2**Position of the spinal cord segments within the cervical, cranial thoracic, and lumbar vertebrae. The cervical intumescence (C6-T2) and the lumbar intumescence (L4-S3) are highlighted.



TABLE 70-2

Localization of Spinal Cord Segments Within Vertebral Bodies in the Dog

SPINAL CORD SEGMENT	VERTEBRAL BODY
C1-C5	C1-C4
C6-T2	C4-T2
T3-L3	T2-L3
L4	13-14
L5, L6, L7	L4-L5
\$1-\$3	L5
Caudal	L6-L7
Cauda equina spinal nerves	L5-sacrum

site of exit immediately caudal to the vertebra of the same number and are susceptible to compressive damage in the lumbosacral region (see the discussion of cauda equina syndrome.

Once spinal cord lesions are localized to the proper regional spinal cord segments and vertebrae, further diagnostic testing will usually be necessary to establish an etiology. Radiographs should be taken of the vertebral bodies that house the affected spinal cord segments. Vertebral radiographs may identify vertebral malformations, subluxation caused by trauma, diskospondylitis, vertebral fractures, intervertebral disk disease, and lytic vertebral neoplasms. A

myelogram or other diagnostic imaging technique (e.g., computerized tomography [CT], magnetic resonance imaging [MRI]) may be performed to identify a compressive or expansive lesion in the spinal canal. Cerebrospinal fluid analysis can be performed to look for evidence of neoplasia or inflammation. When systemic infectious or neoplastic disorders are considered as differentials for a myelopathy, ancillary tests such as thoracic and abdominal radiographs, abdominal ultrasound, lymph node aspirates, complete ophthalmic examination, serology, and tissue biopsies may be helpful in determining the diagnosis. Rarely, surgical exploration of the spinal cord at the affected site will be required to achieve a diagnosis, gauge prognosis, and recommend treatment.

# **ACUTE SPINAL CORD DYSFUNCTION**

# TRAUMA

Traumatic injuries to the spinal canal are common, with fractures and luxations of the spine and traumatic disk extrusion being most frequent. Severe spinal cord bruising and edema can occur secondary to trauma, even without disruption of the bony spinal canal.

#### **Clinical Features**

The clinical signs associated with spinal trauma are acute and generally nonprogressive. Animals are usually in pain, and other evidence of trauma (e.g., shock, lacerations, abrasions, fractures) may be present. Neurologic findings depend on lesion location and severity. Neurologic examination should determine the location and extent of the spinal injury. Excessive manipulation or rotation of the animal should be avoided until the vertebral column is determined to be stable.

## **Diagnosis**

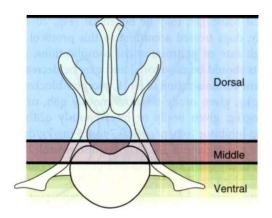
The diagnosis of trauma is readily made on the basis of the history and physical examination findings. A thorough and rapid physical examination is important to determine whether the animal has life-threatening, nonneurologic injuries that should be addressed immediately. Concurrent problems may include shock, pneumothorax, pulmonary contusions, diaphragmatic rupture, ruptured biliary system, ruptured bladder, orthopedic injuries, and head trauma. Concern that the animal may have vertebral column instability warrants the use of a stretcher or board to restrain, examine, and transport the dog or cat in lateral recumbency.

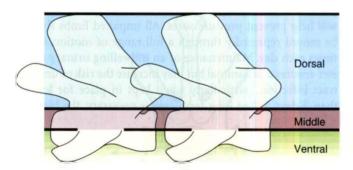
The neurologic examination can be performed with the animal in lateral recumbency but will be limited to evaluation of mental status, cranial nerves, posture, muscle tone, voluntary movement, spinal reflexes, the cutaneous trunci reflex, and pain perception. Dogs with severe thoracic spinal cord lesions may exhibit the Schiff-Sherrington posture (see Fig. 63-8). The most important prognostic indicator after spinal trauma is the presence or absence of nociception or deep pain sensation. If deep pain is absent caudal to a traumatic spinal cord lesion, the prognosis for return of neurologic function is poor.

The neurologic examination allows determination of the neuroanatomic site of the lesion. Survey radiographs can then be used to more specifically localize the lesion, assess the degree of vertebral damage and displacement, and aid in prognosis. Manipulation or twisting of unstable areas of the spine must be avoided during radiography. If the animal is recumbent or restrained on a board, then lateral and crosstable ventrodorsal views allow assessment for the presence or absence of fractures or an unstable vertebral column. CT is a more accurate means to assess vertebral damage.

The *entire* spine should be assessed radiographically. Most spinal fractures and luxations occur at the junction of mobile and immobile regions of the spine, such as the lumbosacral junction or the thoracolumbar, cervicothoracic, atlantoaxial, or atlantooccipital regions. LMN lesions at an intumescence can mask a UMN lesion located more cranially in the spinal cord; therefore radiographic and clinical evaluation are important. Myelography, CT, or MRI should be used to look for radiographically inapparent lesions when radiographic lesions do not correspond with neuroanatomic localization.

Various classification schemes exist to determine the stability of vertebral injuries and the need for surgery. The vertebral body can be divided into three compartments and each assessed using radiographs or CT for damage (Fig. 70-3). When two of the three compartments are damaged or displaced, the fracture is considered unstable. Unstable





#### FIG 70-3

Illustration of the three-compartment model for radiographic evaluation of spinal fractures. The dorsal compartment includes the articular facets, laminae, pedicles, spinous processes, and supporting ligaments. The middle compartment contains the dorsal longitudinal ligament, the dorsal annulus, and the floor of the spinal canal. The ventral compartment consists of the remainder of the vertebral body and the annulus, the nucleus pulposus, and the ventral longitudinal ligament. When two or three of the compartments are damaged or displaced, surgical stabilization is indicated.

fractures require surgical intervention or splinting, whereas stable fractures without significant ongoing spinal cord compression are managed conservatively. Splints are most effective when deep pain sensation is present, when ventral and middle compartments are intact, and when associated soft tissue injuries are minimal. Most dogs with cervical or lumbosacral injury are managed nonsurgically unless the patient deteriorates neurologically or remains in a great deal of pain 72 hours after injury, which suggests nerve root entrapment. Surgery is preferred for unstable thoracic and lumbar injuries.

#### **Treatment**

Primary treatment of animals with acute spinal injury involves evaluation for and treatment of other life-threatening injuries and maintenance of patient blood pressure, perfusion, and oxygenation. There is some evidence that the immediate IV administration of methylprednisolone sodium succinate (MPSS), a highly soluble corticosteroid with neuroprotective effects exerted primarily by its actions as a free

radical scavenger, may be beneficial (Fig. 70-4). Unfortunately, dogs treated according to this protocol suffer from a high rate of gastrointestinal complications, and adverse effects should be monitored and may be decreased by concurrent administration of an  $H_2$ -receptor blocker (ranitidine 2 mg/kg, given orally or intravenously q8h, or famotidine 0.5 mg/kg, given orally or intravenously q24h), a proton pump inhibitor (omeprazole 0.7 to 1.5 mg/kg/day) or a synthetic prostaglandin E1 analog (misoprostol 2 to 5  $\mu$ g/kg, given orally q8h), and a mucosal protectant (sucralfate 0.25 to 1 g, given orally q8h; see Chapter 30).

Intensive nursing care is critically important in dogs and cats managed conservatively or surgically. Narcotic analgesics may be administered as needed (Table 70-3). Thickly padded, clean, dry cages and frequent turning of the patient will help prevent pressure sores. All impaired limbs should be moved repeatedly through a full range of motion many times each day. Maintenance of an indwelling urinary catheter ensures a dry animal but may increase the risk of urinary tract infection, particularly when kept in place for longer than 3 days. When long-term care is necessary, the bladder

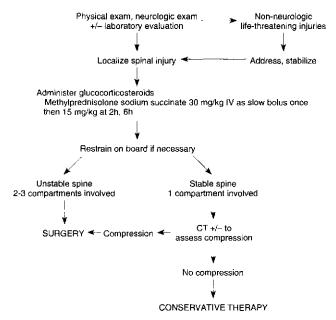


FIG 70-4
Algorithm for the management of acute spinal trauma.



Narcotic Analgesics Used to Treat Spinal Pain in Dogs

DRUG	DOSAGE
oxymorphone	0.05 mg/kg IM
morphine	0.3-2.2 mg/kg SC or IM
butorphanol	0.4-0.8 mg/kg SC
buprenorphine	0.02-0.06 mg/kg IM or SC

IM, Intramuscular; SC, subcutaneous.

should be gently expressed or catheterized and emptied four to six times daily and urinary tract infections treated as they occur. In animals with UMN bladders (see Chapter 63) or those with urethral spasm, medical therapy (phenoxybenzamine 1 mg/kg q8h and diazepam 1.25 to 2.5 mg/kg q8h) may help relax the urethral sphincter, making bladder expression easier and less traumatic. When an animal starts to regain voluntary motion in the limbs, physical therapy is increased; hydrotherapy or swimming stimulates voluntary movement, improves circulation to the limbs, and cleans the skin.

## **Prognosis**

Prognosis for recovery depends on the site and severity of injury. Unstable cervical vertebral fractures are associated with very high mortality at the time of trauma and also in the perioperative period. Prognosis for recovery is good if affected animals do not die acutely from respiratory dysfunction. Animals with thoracic and lumbar spinal cord injury and intact voluntary motion have a good prognosis for return of full function. Animals that are paralyzed but retain deep pain and normal bladder function have a fair prognosis for recovery, although they may have residual neurologic deficits. Animals presenting with no deep pain sensation rarely recover. Lesions of the white matter producing strictly UMN signs may have a better prognosis for full recovery than lesions affecting clinically important LMNs at the cervical or lumbar intumescence. In any animal with paralysis caused by a spinal cord injury, if no signs of improvement are evident by 21 days after injury, the prognosis for recovery is poor.

# **HEMORRHAGE/INFARCTION**

Nontraumatic hemorrhage into the spinal canal causing acute neurologic deficits and sometimes pain (i.e., hyperesthesia) has been recognized in young dogs with hemophilia A, dogs of any age with von Willebrand's disease, dogs and cats with acquired bleeding disorders (i.e., warfarin intoxication, thrombocytopenia), dogs with vascular anomalies (i.e., aneurysms, arteriovenous fistulas), and dogs and cats with primary or metastatic spinal neoplasia (i.e., lymphoma, hemangiosarcoma). Hemorrhage can be subdural or epidural. Signs occur acutely and are minimally progressive, with neurologic signs reflecting the site and severity of spinal cord damage. Antemortem diagnosis usually requires advanced diagnostic imaging (i.e., MRI), although identification of a systemic bleeding disorder or neoplasia can suggest the diagnosis. In addition to treatment to resolve the cause of bleeding, significant acute spinal cord compression caused by hemorrhage may require surgical decompression.

Spinal cord infarction by a blood clot is a rare cause of peracute neurologic dysfunction in dogs and cats. Signs are referable to the site and severity of the vascular compromise. Blood stasis, endothelial irregularity, hypercoagulability, and impaired fibrinolysis are all known predisposing factors for thromboembolism (see Chapter 12). Cardiomyopathy, hyperadrenocorticism, protein-losing nephropathy, immunemediated hemolytic anemia, heartworm disease, vasculitis,

and disseminated intravascular coagulation have all been associated with an increased risk of systemic thrombosis and can occasionally result in regional spinal cord infarction. Treatment consists of general supportive care and medications to decrease the risk of further infarction; however, antemortem definitive diagnosis is difficult.

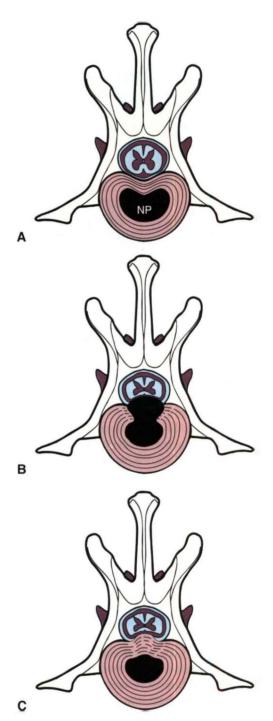
#### **ACUTE INTERVERTEBRAL DISK DISEASE**

The intervertebral disks are composed of an outer fibrous layer (the annulus fibrosus) and a gelatinous center (the nucleus pulposus). With normal aging the nucleus is gradually replaced by fibrocartilage. In some dogs, particularly the chondrodystrophoid breeds, the nucleus matrix degenerates and mineralizes, making these dogs prone to acute disk rupture. Acute extrusion of mineralized nucleus pulposus into the spinal canal through the dorsal annulus causing bruising or compression of the spinal cord is classified as a Hansen's type I disk (Fig. 70-5; for type II disk). This type of disk injury is most common in small breeds of dogs such as the Dachshund, Toy Poodle, Pekingese, Beagle, Welsh Corgi, Lhasa Apso, Shih Tzu, Chihuahua, and Cocker Spaniel, with a peak incidence between 3 and 6 years of age. Acute type I disk extrusions are also occasionally diagnosed in middle-aged large-breed dogs, particularly in Basset Hounds, Labrador Retrievers, Doberman Pinschers with caudal cervical vertebral instability, and German Shepherd Dogs. Intervertebral disk disease is a rare cause of clinically evident spinal cord compression in the cat, with predominantly acute type I disk prolapse occurring in older cats (mean age, 9.8 years) in the lower thoracic and lumbar regions (most commonly, L4/L5).

#### **Cervical Disk Disease**

#### **Clinical Features**

The predominant sign of cervical intervertebral disk disease (IVDD) is neck pain. The discomfort is often severe, and affected dogs may vocalize with the pain of movement. They may stand with their head and neck extended and may be reluctant to eat or drink from dishes placed on the floor. Some affected dogs lift one forelimb while standing to relieve the discomfort of nerve root irritation or cervical muscle spasm; this is called root signature (Fig. 70-6) and can be seen with cervical IVDD at any site. Compression of nerve roots and meninges causes neck pain. The vertebral canal in the cervical region has a very large diameter, such that even when large masses of disk material extrude into the spinal canal, significant spinal cord compression is unlikely. When significant spinal cord compression or concussion does occur, the result is usually UMN paresis or paralysis in all four legs, with rear limbs more severely affected than forelimbs. Caudal cervical disk extrusions (C6/7, C7/T1) can result in LMN forelimb weakness and scapular muscle atrophy together with UMN paresis in the rear limbs. Signs with spinal cord compression by type 1 disks are usually symmetric, although lateralized disk extrusions can result in asymmetry. The C2/3 intervertebral disk is most frequently



#### FIG 70-5

**A**, The normal relationship between the intervertebral disk and the spinal cord. *NP*, Nucleus pulposus. **B**, Hansen type I disk extrusion, wherein the NP herniated into the vertebral canal through a damaged *AF*, annulus fibrosus. **C**, Hansen type II disk protrusion, with bulging of the annulus into the vertebral canal.

involved, with the prevalence progressively decreasing from C3/4 to C7/T1. The C6/7 disk is more commonly affected in large-breed dogs as a component of cervical vertebral malformation malarticulation syndrome (also known as wobbler syndrome).



**FIG 70-6**Adult Beagle with neck and shoulder pain secondary to cervical intervertebral disk prolapse. Lifting of the limb has been referred to as *root signature*.



Cervical disk disease should be suspected on the basis of the signalment, history, physical examination, and neurologic findings. Most affected dogs show obvious signs of pain, but some stoic dogs do not exhibit discomfort during neck movement or manipulation. There should be no systemic signs of illness (e.g., fever, weight loss), and no specific neurologic abnormalities suggesting intracranial disease. Important differential diagnoses for dogs with neck pain include meningitis, diskospondylitis, vertebral neoplasia, polyarthritis, myositis, and trauma (see Box 69-1). Acute neurologic dysfunction caused by cervical disk disease must be distinguished through testing from cervical fracture/luxation, hemorrhage, or fibrocartilagenous embolism.

Spinal radiographs can be taken in an awake animal to look for evidence of disk disease and rule out other diseases (e.g., diskospondylitis, lytic vertebral tumor, fracture, atlantoaxial luxation). In animals with clinical features making surgery likely if disk extrusion is confirmed, radiographs are best obtained under general anesthesia to facilitate the optimal positioning and imaging necessary to detect subtle lesions.

Observation of calcified disk spaces confirms the presence of generalized intervertebral disk disease, but unless there is dorsal displacement of mineralized disk material into the spinal canal, this does not necessarily implicate the disk extrusion as the cause of neurologic dysfunction. Narrowing of the affected intervertebral space is commonly recognized (Fig. 70-7). Myelography or advanced diagnostic imaging (i.e., CT, MRI) are necessary to make a definitive diagnosis and determine which disk space is involved before surgical treatment. Myelography is the least expensive option, but it is also the most invasive and the least likely to provide later-

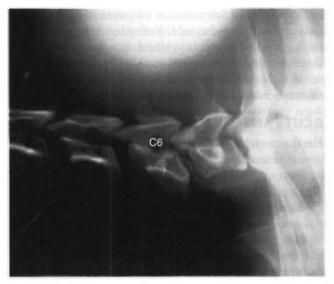


FIG 70-7
Lateral radiograph of the cervical vertebral column of an adult dog showing acute intervertebral disk prolapse at C6-C7 site. The intervertebral space is narrowed, and a calcified density can be seen in the spinal canal above the disk space.



TABLE 70-4

Classification of Dysfunction and Treatment Recommendations: Canine Cervical Disk Extrusion

GRADE	CLINICAL FINDINGS	TREATMENT
1	Single episode of pain	Cage rest
	Normal neurologic exam	+/- analgesics
2	Intractable pain or	Surgical
	Recurrent pain	Decompression
3	Neurologic deficits	Surgical
	+/- pain	Decompression

alizing information. Analysis of cerebrospinal fluid (CSF) should always precede myelography, to rule out inflammatory central nervous system (CNS) disease (see the discussion of myelography, Chapter 64). CSF changes associated with disk extrusion are usually minimal but may include very slight increases in protein concentration and cell count. CT and MRI may be used to further delineate a compressive disk lesion identified myelographically, or they may be used as the sole technique for detecting and characterizing a disk lesion, particularly in regions where myelographic interpretation can be difficult and precise anatomic localization is important (e.g., caudal cervical; Fig. 70-8).

#### **Treatment**

Treatment decisions in dogs with cervical disk disease are based on the severity of disease noted at the time of presentation (Table 70-4). Dogs with a single episode of acute neck



FIG 70-8
A 7-year-old Dachshund (A) with a 3-week history of severe neck pain and mild proprioceptive deficits in the left rear limb. Magnetic resonance imaging (MRI) revealed prolapse of the C3-C4 intervertebral disk, with significant spinal cord compression at that site (B).

pain and no neurologic deficits are usually managed conservatively with strict cage confinement and analgesics. Animals should be kept in a small kennel crate or in the owner's arms at all times except when walked outside with a harness to urinate and defecate. Nonsteroidal anti-inflammatory drugs or narcotic analgesics (see Table 70-3) can be administered for the first 3 to 5 days if strict confinement is likely to be enforced. Muscle relaxants (methocarbamol 15-20 mg/kg, administered orally q8h) will also decrease painful muscle spasms. After 3 to 4 weeks of strict crate confinement, 3 weeks of house confinement with no jumping or running and leash exercise should be recommended followed by a gradual increase in monitored exercise and (if necessary) a weight reduction program.

Most dogs with neck pain and no neurologic deficits respond initially to this conservative medical management, but a few will have intractable pain. Approximately 40% of responding dogs will experience recurrent episodes of pain in the future. Dogs with cervical pain that does not resolve

in 1 or 2 weeks, dogs with severe pain that cannot be controlled, dogs with recurrent episodes of neck pain, and dogs that develop paresis or paralysis indicating cervical spinal cord compression should be treated surgically. Even if cervical pain is the only clinical finding, most dogs with cervical intervertebral disk prolapse have a large amount of disk material within the spinal canal and these dogs will have a more complete and rapid recovery if surgery is performed. Myelography or MRI to locate the lesion and prompt surgical decompression using a ventral slot procedure are recommended. When the width of the ventral slot required to remove caudal cervical disk material is greater than 30% of the vertebral width, stabilization with a bone graft is recommended to prevent subluxation. Some surgeons recommend prophylactic fenestration of multiple cervical sites whenever a ventral slot surgery is performed to prevent further disk material prolapse and reduce the recurrence rate, but this is controversial. Most dogs are in a great deal less pain within 24 to 36 hours after decompressive surgery, and resolution of neurologic deficits occurs gradually over 2 to 4 weeks. Exercise is restricted for 2 weeks, followed by physiotherapy to enhance recovery. The prognosis for full recovery in dogs with neck pain alone or neck pain plus moderately severe tetraparesis is 80% to 90% at 4 weeks. Dogs with paralysis are more likely to have residual deficits, but approximately 80% of these dogs will become ambulatory. Rarely, vertebral subluxation occurs after ventral slot surgery, causing neck pain and worsening of neurologic deficits. Re-imaging (MRI preferred) followed by surgical distraction and stabilization is required in these dogs, which should result in a good prognosis for recovery.

# **Thoracolumbar Disk Disease**

#### **Clinical Features**

Most dogs with thoracolumbar disk disease are presented because of back pain and rear limb paresis or paralysis. The back pain in these dogs is usually less severe than that noted with cervical IVDD, but affected dogs may stand with an arched back and resent abdominal compression or palpation. The diameter of the vertebral canal is relatively small in the thoracolumbar region, so even small volumes of disk material extruded into the canal cause spinal cord compression and neurologic deficits. In addition to the compressive effect of the disk material, it is common to have impact injury to the spinal cord from explosive disk rupture. Most (>50 percent) of the disk extrusions in this region occur at the T12/13 or T13/L1 site, with 85% between T11/12 and L2/3. Disk extrusions at these sites cause UMN paresis or paralysis in the rear limbs. Only 10% to 15% of dogs will have a disk extrusion between the L3/4 and L6/7 disks, damaging the spinal cord at the lumbar intumescence and resulting in LMN signs.

The severity of the initial signs and the speed with which they progress are related not only to the volume of disk material extruded and the degree of resultant spinal cord compression but also to the force of the extrusion (see Fig. 70-1). In some dogs evidence of pain and subtle weakness resulting from partial disk rupture and mild spinal cord compression may be present for a few days or weeks before mild trauma or movement results in the extrusion of more disk material causing paralysis. The neurologic signs observed in dogs and cats with intervertebral disk disease are usually bilaterally symmetric. Affected animals usually exhibit pain on spinal palpation right over the affected disk because of meningeal and nerve root irritation at the site. When spinal cord damage is severe between T3 and L3, the cutaneous trunci reflex (see Fig. 63-17) can be used to further aid in lesion localization.

# **Diagnostic Approach**

Trauma, fibrocartilaginous embolism (FCE), and vertebral neoplasia are the major differential diagnoses considered in animals with acute thoracolumbar disk extrusions. The lesion should be localized as precisely as possible on the basis of neurologic examination findings and detection of a specific area of spinal pain. Spinal survey radiographs can be taken in an awake animal to look for evidence of disk disease and rule out other diseases. Careful positioning of the suspected disk space in the center of the beam, with the dog anesthetized, is necessary for radiographic identification of subtle lesions, but this testing is usually reserved for potential surgical candidates, when preparations have been made for further diagnostic imaging and decompressive surgery during the same anesthetic episode.

Observation of calcified disk spaces confirms the presence of generalized intervertebral disk disease, but radiographs are only between 60% and 70% accurate in identifying the location of thoracolumbar disk extrusion. Radiographic changes consistent with herniation of an intervertebral disk in the thoracolumbar region include a narrowed or wedged disk space, a small or cloudy intervertebral foramen (i.e., "horse's head"), narrowing of the facetal joints, and a calcified density within the spinal canal above the involved disk space (Figs. 70-9 and 70-10).

Myelography or advanced diagnostic imaging (i.e., CT, MRI) should be performed for definitive diagnosis before surgery. CSF is usually collected from the cerebellomedullary cistern before myelography. A cell count can be performed quickly to rule out meningitis/myelitis, and the sample can be saved for further diagnostic testing if the myelogram does not show a compressive lesion. A lumbar injection is preferred for myelography because the contrast medium must sometimes be injected under pressure to get past cord swelling in the area of the disk prolapse. CT is more accurate and faster than myelography; because it is much more reliable at determining what side the disk material is on, it is useful for surgical planning. MRI is superior to CT when extruded disk material is not mineralized and is best for spinal cord evaluation when the diagnosis of disk extrusion is uncertain (see Fig. 70-8). The increased sensitivity of CT and MRI can be problematic because clinically insignificant disk herniations not causing symptomatic spinal cord compression will also be identified.

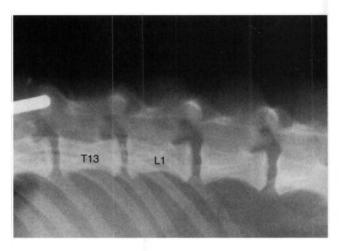


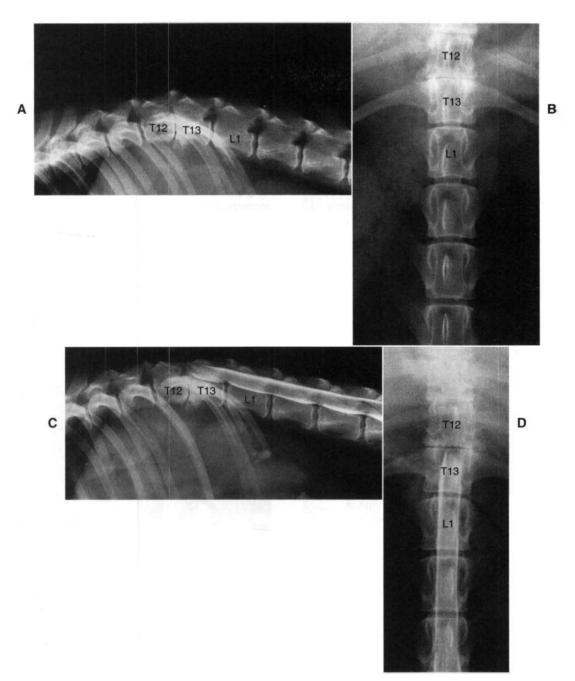
FIG 70-9

Lateral plain radiograph of vertebral column of a 4-year-old Pekingese with acute intervertebral disk prolapse. The intervertebral space between T13 and L1 is narrowed, the intervertebral foramen ("horse's head") is small, and a calcified density can be seen in the spinal canal above the T13-L1 disk space.

#### **Treatment**

Treatment of acute thoracolumbar intervertebral disk extrusion may be nonsurgical or surgical (Table 70-5). Nonsurgical treatment is usually recommended when there are minimal or inapparent neurologic deficits and the dog is still able to rise and walk unassisted. Strict cage rest is the most important aspect of nonsurgical treatment and must be maintained for a minimum of 6 weeks to allow the annulus to repair. Analgesics (see Table 70-3) and antiinflammatory drugs are often administered as for cervical IVDD. Animals being treated nonsurgically must be evaluated frequently for deterioration in neurologic status because these dogs often deteriorate within 6 to 24 hours. If neurologic symptoms do not improve within 5 to 7 days or if even minor deterioration in neurologic status is seen, then surgical therapy is indicated. Persistent or recurrent pain is also an indication for decompressive surgery.

Surgical treatment is recommended for all patients unable to walk at the time of presentation and for all dogs with signs suggesting less severe spinal cord compression (e.g., paresis, pain) if neurologic signs do not rapidly resolve with medical therapy. The rate of recovery is faster after decompression than after nonsurgical treatment, and the likelihood of residual neurologic deficits is decreased. Decompression is usually accomplished through a hemilaminectomy, and disk material is removed from the spinal canal. Preoperative imaging is essential to identify the affected interspace and to determine which side to decompress to gain access to disk material. Because clinical signs and myelography are not always reliable indicators of lateralized disk material, CT or MRI should be performed whenever possible. In addition to surgical decompression, many surgeons recommend concurrent fenestration at adjacent high-risk sites (T11 to L3) to



#### FIG 70-10

Lateral **(A)** and ventrodorsal **(B)** plain radiographs of the vertebral column of an 8-year-old Miniature Schnauzer with acute paralysis after a chronic history of intermittent back pain. Marked collapse of the intervertebral space at T12-T13, a small intervertebral foramen, and clouding of the foramen is evident. The T13-L1 space is also slightly narrowed. **C** and **D**, Myelography confirms the presence of a significant extradural mass at T12-T13, located ventrally and on the right, causing considerable cord compression and displacement. A minimal extradural mass effect exists as well at T13-L1 without significant compression. Surgery confirmed spinal cord compression by the disk material at T12-T13.

help decrease the likelihood of subsequent herniations in dogs with generalized thoracolumbar disk disease.

Postsurgically, animals must be kept clean and confined. Pressure sores should be prevented in paralyzed patients through the use of padded bedding and frequent turning. Complete bladder emptying at least four times daily by

manual expression, an indwelling catheter, or intermittent aseptic catheterization is necessary in dogs that have lost bladder function. In dogs with UMN bladders medical treatment with phenoxybenzamine and diazepam can lower sphincter pressure, facilitating manual expression and attempts by the animal to void. Massage of the limbs and

passive physiotherapy, including limb abduction, may help prevent neurogenic atrophy and muscle fibrosis in the paraplegic animal. Towel walking of paraparetic dogs can improve attitude and promote early use of the affected limbs. Once the skin incision has healed, swimming may be instituted to encourage movement. In dogs with a prolonged anticipated recovery period, use of a paraplegic cart can provide a stimulus for recovery (Fig. 70-11). Improvement in neurologic function usually occurs within 1 week of surgery. No improvement after 21 days signals that the prognosis for recovery is poor.

More than 90% of dogs with deep pain perception at the time of evaluation recover fully after effective decompression (Table 70-6). The best surgical results are obtained when decompression can be accomplished within 48 hours of the onset of neurologic signs. Dogs with very rapid progression to paralysis (grade 4 or grade 5) over less than 4 to 6 hours should be treated as a surgical emergency and decompressed

without delay. There may be some benefit to preoperative treatment of this group of patients with methylprednisolone sodium succinate, as described for spinal trauma patients if they are presented within 8 hours of the onset of paralysis. This treatment is controversial insofar as the benefits are not well established and adverse effects are common. Dogs with loss of deep pain perception (grade 5) are very unlikely to recover without surgical intervention, but with rapid decompression (within 72 hours) 60% of small-breed dogs and 25% of large-breed dogs will make a functional recovery. If deep pain does not return within 4 weeks, the prognosis for recovery is very poor.

Acute, forceful, intervertebral disk extrusions sometimes cause considerable intramedullary hemorrhage and edema. In approximately 10% of dogs presenting for a rapid onset of complete paralysis and loss of deep pain perception, focal spinal cord damage and edema result in spinal cord ischemia and progressive myelomalacia of the cord cranial and caudal



# TABLE 70-5

Classification of Dysfunction and Treatment Recommendations: Canine Thoracolumbar Disk Extrusion

CLINICAL FINDINGS	TREATMENT
Single episode of pain Normal neurologic exam Intractable pain or	Cage rest +/– analgesics Surgical
Recurrent pain or  Deterioration in neurologic status	Decompression
Ataxia, proprioceptive deficits Paraparesis, able to stand and walk	Cage rest +/- analgesics
Severe paraparesis unable to stand and walk Paralyzed	Surgical Decompression Surgical
	Decompression



#### FIG 70-11

The use of a paraplegic cart can provide a stimulus for recovery and improve mobility and attitude in paralyzed dogs recovering from thoracolumbar disk surgery.



# **TABLE 70-6**

Results of Treatment for Thoracolumbar Disk Disease

NEUROLOGICAL GRADE	CONSERVATIVE % SUCCESS	CONSERVATIVE RECOVERY TIME (WEEKS)	DECOMPRESSION % SUCCESS	DECOMPRESSION RECOVERY TIME (WEEKS)
1 no deficits	>95%	3	>95%	<2
2 paresis (walking)	84%	6	95%	<2
paresis (not walking)	84%	6	93%	<2
4 paraplegia	81%	9-12	95%	1-4
5 no deep pain	<10%		64%	5-10

to the original lesion (i.e., ascending descending myelomalacia). This condition usually develops within 5 days of the original disk extrusion. This disorder should be suspected when the line demarcating the loss of the cutaneous trunci reflex moves cranially or the patellar and withdrawal reflexes are lost (LMN signs) in the rear limbs of a dog that previously had UMN paralysis in the rear limbs after disk extrusion. Most affected dogs are also very anxious and experience a great deal of pain. When ascending descending myelomalacia is recognized, euthanasia should be recommended because no chance for recovery exists and most affected dogs will die within a few days of respiratory paralysis.

#### FIBROCARTILAGINOUS EMBOLISM

Acute infarction and ischemic necrosis of the spinal cord parenchyma occur when fibrocartilage identical to that in the nucleus pulposus of the intervertebral disks is embolized into the very small arteries and veins supplying the spinal cord parenchyma and leptomeninges. This very acute, nonprogressive phenomenon can affect any region of the spinal cord and result in paresis or paralysis. The cause of this disorder is unknown. It is most common in medium-sized and large-breed dogs. It has also been described in smallbreed dogs (especially the Miniature Schnauzer) and a few cats. Most affected dogs are middle aged, with the majority of cases between 3 and 7 years of age. A few dogs younger than 1 year of age have been recognized with FCE, especially Irish Wolfhounds. No gender predilection exists.

#### **Clinical Features**

The onset of neurologic signs is very sudden, and signs may worsen for 2 to 6 hours. In approximately half of all cases, FCE occurs immediately after minor trauma or during exertion. Neurologic examination reflects a focal spinal cord lesion, and the deficits observed depend on the region of spinal cord affected and the severity of cord involvement. The thoracolumbar cord (causing UMN signs in the rear limbs) and the lumbosacral intumescence (causing LMN signs in the rear limbs) are most often affected. The cervical cord is affected less frequently, but it is the site most often affected in small-breed dogs. Neurologic dysfunction may be mild or severe. Asymmetry is common, with the right and left sides affected to different degrees. Dogs commonly cry out as though in pain at the onset of signs, and dogs evaluated within 2 to 6 hours of onset sometimes exhibit focal spinal hyperpathia (i.e., painfulness); however, this resolves quickly, and most affected dogs do not exhibit pain by the time they are brought to a veterinarian, even on manipulation of their spine. The lack of pain and the asymmetry are very helpful in differentiating FCE from other disorders that cause acute nonprogressive neurologic dysfunction, such as acute intervertebral disk extrusion and fracture/luxation.

# **Diagnosis**

FCE is suspected on the basis of the signalment, history, and recognition of acute, nonprogressive, nonpainful spinal cord dysfunction. Radiographs are normal in dogs and cats with



FIG 70-12

This adult Border Collie had an acute onset of lameness, decreased conscious proprioception, and hyporeflexia in the left rear limb while retrieving a Frisbee. The limb was not painful, and radiographs, cerebrospinal fluid (CSF) analysis, and myelogram were all normal. A presumptive diagnosis of fibrocartilaginous embolism (FCE) involving the lumbar and sacral spinal cord segments on the left side was made. This dog recovered uneventfully within a 3-week period.

FCE but assist in ruling out diskospondylitis, fractures, lytic vertebral neoplasia, and IVDD. CSF is usually normal, although an increase in protein (especially albumin) concentration may be observed in some (50%) cases. In the first 24 hours after the onset of clinical signs, a few dogs have a mild increase in neutrophil numbers within the CSF. Myelography is usually normal, although some animals exhibit focal intramedullary cord swelling. Myelography is most useful to rule out compressive lesions of the spinal cord for which surgery might be indicated, such as fractures, disk extrusion, and neoplasia.

CT is not useful in the diagnosis of FCE beyond excluding a compressive myelopathy. MRI may reveal focal cord density changes in severely affected dogs, but mild lesions will not be evident. The diagnosis of FCE be made only on the basis of clinical findings and exclusion of compressive and inflammatory acute spinal cord disorders (Fig. 70-12).

#### **Treatment**

Treatment for FCE consists of nonspecific supportive measures and nursing care, as described for paralyzed dogs. Most affected dogs are large breeds, making this type of management difficult. In animals brought to the clinician during the first 6 hours of paralysis, it may be reasonable to treat aggressively with one dose of methylprednisolone sodium succinate, as recommended for the initial treatment of acute spinal cord trauma (see Figure 70-4). Most clinical improvement takes place within the first 7 to 10 days after the onset of neurologic signs, although it may take 6 to 8 weeks for a complete return to function. If no improvement is seen within 21 days, it is unlikely that the dog or cat will improve.

## **Prognosis**

Recovery depends on the extent and location of spinal cord injury. The prognosis is best for recovery in dogs and cats with intact deep pain sensation and strictly UMN signs, including increased muscle tone and hyperactive reflexes. When the spinal cord is damaged at the brachial or lumbosacral intumescence (C6 to T2 or L4 to S3), causing LMN signs, a full recovery is less likely.

#### ATLANTOAXIAL INSTABILITY

Because many dogs with congenital atlantoaxial instability have slowly progressive waxing and waning tetraparesis, this condition will be discussed with chronic progressive spinal cord disease. Traumatic fracture of the dens leading to subluxation can occur in any dog or cat and will result in acute UMN dysfunction in all limbs.

## **NEOPLASIA**

Neoplasms usually cause neurologic signs by compressing or infiltrating the spinal cord parenchyma. Neoplastic conditions will be discussed in this chapter with chronic progressive spinal cord diseases. Occasionally, neoplasia will cause acute nonprogressive neurologic signs as a result of tumoror metastasis-associated intraparenchymal hemorrhage or lysis of vertebral bones, leading to fracture.

# PROGRESSIVE SPINAL CORD DYSFUNCTION

Damage to the spinal cord that progresses over a few days to weeks (subacute) is most often caused by inflammatory (infectious or immune) processes or some type of neoplasia. Degenerative disorders and most cancers generally cause more slowly progressive spinal cord dysfunction. In all patients with progressive spinal cord dysfunction complete patient evaluation, including systemic evaluation for extraneural disease, should be recommended. The lesion should be localized and ancillary tests performed to reach a diagnosis and determine appropriate treatment.

# **SUBACUTE PROGRESSIVE DISORDERS**Infectious Inflammatory Disease

Most of the infectious inflammatory diseases discussed in Chapter 69 can result in myelitis (i.e., spinal cord inflammation), leading to progressive neurologic signs suggesting multifocal or focal spinal cord damage. CSF analysis is necessary to confirm that inflammatory disease is present. Additional diagnostic tests may be necessary to identify an etiology (see Chapter 69).

# **Noninfectious Inflammatory Disease**

Noninfectious inflammatory diseases, specifically granulomatous meningoencephalitis (GME), steroid-responsive meningitis arteritis (SRMA), and feline polioencephalomyelitis, can affect the spinal cord. Cervical pain is a constant feature of SRMA, but neurologic deficits suggesting spinal cord parenchyma damage with this disorder are rare. Neurologic deficits are common, however, with focal or disseminated GME affecting the spinal cord. CSF analysis is necessary to confirm inflammatory myelitis, and additional tests are required to rule out infectious etiologies. See Chapter 69 for more information on these syndromes.

# **Diskospondylitis**

Diskospondylitis is an infection of the intervertebral disks and adjacent vertebral endplates by bacterial or fungal organisms. Hematogenous spread of infection from infected foci in the body, extension from an infected local site, and migration of inhaled plant material (grass awns) have all been implicated. Numerous causative organisms have been isolated, with the most common being *Staphylococcus intermedius*, *Streptococcus* spp., and *Escherichia coli*. *Brucella canis* is less common but should be tested for because of human health implications. The fungal organisms *Aspergillus terreus* (in German Shepherd Dogs) and *Paecilomyces varioti* have been isolated from diskospondylitis lesions in a few dogs. *Actinomyces* spp. are commonly implicated in L2-L4 diskospondylitis caused by migration of inhaled grass awns.

Diskospondylitis occurs most often in young and middleaged medium- to large-breed dogs. German Shepherd Dogs and Labrador Retrievers may have an increased prevalence of this disorder. Diskospondylitis is very rarely diagnosed in cats. Males are affected more often than females in both species.

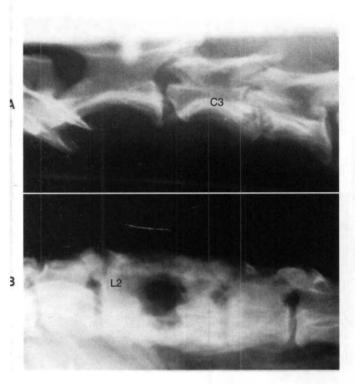
# **Clinical Features**

Spinal pain is the most common initial clinical sign of diskospondylitis. Palpation of the affected region of the spine usually allows lesion localization. Systemic signs such as fever, anorexia, depression, and weight loss occur in 30% of affected dogs, but hematologic inflammatory changes are rarely observed unless there is concurrent endocarditis or some other systemic infection. Secondary (i.e., reactive) polyarthritis may occur (see Chapter 74), resulting in a generally stiff, stilted gait in some dogs.

Neurologic deficits in dogs and cats with diskospondylitis are extremely uncommon. In chronic or untreated cases neurologic dysfunction can result from spinal cord compression by proliferating inflammatory tissue or from pathological fracture of lytic vertebrae. Occasionally, severe inflammation in the bone will cause functional abnormalities in the overlying spinal cord without any cord compression.

#### Diagnosis

The diagnosis of diskospondylitis is suspected after physical examination and confirmed by radiographic examination of the affected vertebrae. Radiographic changes of diskospondylitis characteristically include narrowing of the disk space, irregularity or lysis of one or both vertebral end plates (especially ventrally), sclerosis at the margins of bone loss, and osseous proliferation of adjacent vertebral bone (Fig. 70-13). The most commonly affected sites are the midthoracic,



#### FIG 70-13

**A**, Lateral radiograph of cervical vertebral column of adult dog showing diskospondylitis between the third and fourth cervical vertebrae (C3 and C4). **B**, Lateral radiograph of lumbar vertebral column of an adult Pointer showing severe chronic diskospondylitis between the second and third lumbar vertebrae (L2 and L3).

caudal cervical, thoracolumbar, and lumbosacral spine. It is common for diskospondylitis to affect more than one disk space (Fig. 70-14), so survey radiographs of the entire spine are recommended. Radiographic signs of diskospondylitis may not be apparent for several weeks after the onset of clinical signs. MRI or CT can identify subtle endplate erosion before radiographically apparent lesions are visible.

Blood culture is the most rewarding noninvasive method of isolating the organism responsible for the vertebral infection, yielding the organism in approximately half of the cases. Echocardiography and urine culture should be performed to evaluate the cardiac and urogenital systems as potential sources of infection. Percutaneous needle aspiration of the infected disk during general anesthesia using fluoroscopy has been effective in yielding positive cultures in some cases with negative blood and urine cultures, but this technique is usually reserved for cases in which other culture techniques have yielded negative results and the response to an empirically selected antibiotic is inadequate. A spinal needle is guided into the disk space using fluoroscopy or CT, and a small amount of sterile saline (0.3 to 0.5 ml) is injected and then aspirated for culture. Brucella serology or polymerase chain reaction (PCR) should be considered in all affected dogs because of the public health significance of brucellosis (see Chapter 58), despite its very low prevalence (<10%) in the United States and Canada.

#### **Treatment**

Initial treatment of diskospondylitis consists of antibiotics, cage rest, and analgesics. If an organism is isolated, susceptibility testing should guide antibiotic therapy. If an organism is not found, initial treatment attempts should be directed against Staphylococcus spp. Bactericidal antibiotics with a spectrum against gram-positive organisms and the ability to concentrate in bone are recommended. Firstgeneration cephalosporins (cefazolin 25 mg/kg, given intravenously q8h, cephalexin 22 mg/kg, given orally q8h) and amoxicillin with clavulanate (Clavamox 12.5 to 25 mg/kg, given orally q8h) have been effective. Quinolones can be added if gram-negative organisms are suspected. Ampicillin is the antibiotic of choice for Actinomyces infections associated with grass awn migration. Antibiotics are administered parenterally for the first 3 days whenever neurologic deficits are present, and then oral administration is continued for at least 8 weeks and up to 6 months, if necessary.

In addition to antibiotic therapy, the patient's activity should be restricted to minimize discomfort and decrease the chance of pathologic fracture and luxation. Analgesics may be administered for 3 to 5 days, but their use will make it difficult to assess the efficacy of antibiotic therapy and may make it more difficult to enforce strict cage rest. Most dogs show very rapid clinical improvement within the first week of treatment. Dogs treated medically should be reevaluated clinically and radiographically every 3 weeks. With time, the lytic process should resolve and the affected vertebrae should fuse. Antibiotics should be administered for a minimum of 8 weeks. Antibiotics may then be discontinued if the spine is no longer painful over the affected sites and there is no radiographically visible lysis. Most treated animals do not relapse, unless the diskospondylitis is caused by a grass awn foreign body.

# CHRONIC PROGRESSIVE DISORDERS Neoplasia

Tumors that grow and compress or infiltrate spinal cord parenchyma frequently cause chronic, progressively worsening signs of spinal cord dysfunction. Spinal tumors can be primary or metastatic. The most common tumors affecting the spinal cord in the dog are extradural tumors arising from the vertebral body (e.g., osteosarcoma, chondrosarcoma, fibrosarcoma, myeloma) and extradural soft tissue tumors, including metastatic hemangiosarcoma, carcinoma, liposarcoma, and lymphoma. Intradural extramedullary tumors such as meningiomas, neuroepithelioma, and peripheral nerve sheath tumors are also common, comprising 35% of all spinal tumors. Intramedullary tumors (i.e., astrocytomas, ependymomas, metastatic tumors) are relatively rare in the dog, with the exception of metastatic hemangiosarcoma. Lymphoma can be extradural, intradural/extramedullary, or intramedullary in the dog and is usually a manifestation of multicentric disease. Extradural lymphoma is the only common spinal tumor in the cat.

Spinal tumors occur with equal frequency in males and females and can occur in any breed of dog or cat, although



**A,** A 5-month-old Boxer puppy with back pain resulting from diskospondylitis. **B** and **C,** Lateral spinal radiographs reveal lesions at T8-T9 and L2-L3, with destruction of adjacent vertebral body end plates, collapse of the intervertebral disk spaces, shortening of the vertebral bodies, and new bone production around the ends of the affected vertebral bodies.

large-breed dogs are most often affected. Most spinal cord tumors are found in middle-aged and older dogs, with the mean age at the time of diagnosis being 5 to 6 years. Two noteworthy exceptions are lymphoma, which can affect dogs of any age, and neuroepithelioma, a primary intradural extramedullary tumor that has a predilection for T10 to L1 in young dogs, particularly German Shepherd Dogs and Golden Retrievers. In addition, vertebral osteomas may occur in young dogs and result in spinal cord compression, as can cartilaginous exostoses, benign proliferative lesions of the bone indistinguishable from neoplasia except by biopsy (Fig. 70-15; see also see Fig. 64-7). Spinal lymphoma is most common in young (mean age, 4 years) adult feline leukemia (FeLV)-positive cats. Certainly, spinal neoplasia cannot be eliminated as a differential diagnosis strictly on the basis of signalment.

#### **Clinical Features**

Clinical signs are usually insidious and related to the location of the tumor. Early diagnosis is difficult because neurologic abnormalities are not clinically apparent until there has been significant compression or destruction of the spinal cord. Many animals have months of slowly progressive clinical signs before a diagnosis is made. Pain may be a prominent feature in dogs and cats with nerve root tumors encroaching on the spinal cord, tumors involving the meninges, and aggressive tumors involving vertebral bone. Progressively worsening lameness and pain on limb manipulation (i.e., radicular pain, root signature) without initial neurologic deficits are common in dogs with peripheral nerve sheath tumors involving nerve roots in the cervical or lumbar intumescence. An ipsilateral Horner's syndrome and/or loss of the panniculus reflex may be seen if the thoracic nerve roots are involved. Pain is not a common feature of intramedullary spinal cord primary tumors or metastases. Although animals with compressive lesions of the T3-L3 spinal cord typically maintain urinary and fecal continence until after the limbs are paralyzed, some animals with intramedullary neoplasms will become incontinent while still able to walk.

Differential diagnoses must include other disorders that cause slowly progressive neurologic dysfunction, including type II disk protrusion and degenerative myelopathy (DM). Rapidly growing extradural tumors such as lymphoma and primary or metastatic intramedullary tumors sometimes

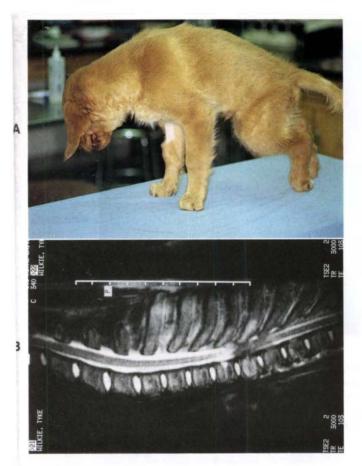


FIG 70-15

**A,** A 3-month old Golden Retriever puppy with spinal pain and progressive upper motor neuron (UMN) signs in both rear limbs resulting from a vertebral osteoma. **B,** Magnetic resonance imaging (MRI) showing severe compressive spinal cord damage from the caudal aspect of the T4 vertebral body extending caudally through the T6 vertebral body.

cause rapidly progressive neurologic signs more typical of inflammatory myelitis. Acute paresis/paralysis may be seen in dogs or cats with tumor-associated hemorrhage or vertebral pathologic fractures.

#### **Diagnosis**

Whenever a neoplasm is considered as a differential diagnosis for spinal cord dysfunction, a thorough physical examination and clinicopathologic evaluation are necessary to look for sites of primary tumor and evidence of associated systemic disease. Fundic examination, palpation of lymph nodes, and rectal examination should be performed, as well as thoracic and abdominal radiographs, to identify a primary tumor site or metastasic lesions. Ultrasonographic examination of the spleen, liver, and heart should be performed in dogs whenever metastatic hemangiosarcoma is possible. Aspiration of the lymph nodes, spleen, and/or liver and examination of peripheral blood or bone marrow smears may yield the diagnosis in dogs with lymphoma. Patients with multiple myeloma often secrete paraproteins, causing a hyperproteinemia and a monoclonal gammopathy. Most

cats with spinal lymphoma are FeLV-positive (>80%), and many have obvious systemic disease and hematologic evidence of bone marrow involvement.

Survey radiographs of the affected region of the spine are recommended. Bony changes will be seen primarily with vertebral tumors, in which obvious osteolysis or bone proliferation is common (Fig. 70-16). When a region of lysis is identified, fine needle aspiration of the lesion sometimes yields a diagnosis. The entire axial and appendicular skeleton should be surveyed for lytic lesions if clinical findings make multiple myeloma likely. Soft tissue tumors of the spinal cord are almost never visible using survey radiographs. Myelography is a fairly reliable method to identify, localize, and characterize spinal cord tumors, but it is relatively invasive and provides less useful diagnostic information than advanced imaging techniques such as CT and MRI. CSF analysis should always precede myelography. With tumors compressing the spinal cord, CSF analysis typically reveals nonspecific changes, including slight increases in protein concentration and a mild mononuclear pleocytosis. Neoplastic cells are rarely identified, except in cats and dogs with lymphoma (Fig. 70-17).

Myelography allows most spinal cord tumors to be characterized as intramedullary, extramedullary-intradural, or extradural (see Fig. 64-6). When available, advanced imaging techniques (i.e., CT, MRI) add valuable information regarding precise tumor location and degree of spinal cord involvement, which may be important when considering surgical treatment and/or radiation therapy.

# **Treatment**

Surgical decompression and attempts at complete tumor excision are usually limited to well-encapsulated intradural extramedullary tumors as a referral procedure. Feline menigiomas may have a good prognosis following surgical excision. Intramedullary tumors cannot usually be treated successfully with surgery because of their intimate involvement with neural tissue.

Chemotherapy and radiation therapy as primary or postoperative adjuvant therapies have met with limited success in the treatment of spinal tumors in dogs and cats. Radiation therapy may be of some benefit in dogs and cats with spinal lymphoma, plasma cell tumors, meningiomas, and some nerve sheath tumors. Corticosteroids, although they have little effect on most tumors, can decrease tumor-associated edema and inflammation and result in remarkable temporary improvement. Lymphoreticular tumors such as lymphoma and myeloma can also be treated with traditional chemotherapy protocols, although only a few of the drugs used cross the blood-brain barrier and the long-term prognosis is poor.

## **Intraspinal Articular Cysts**

Cysts arising from the joint capsule of spinal facetal joints can, through enlargement, cause chronic progressive focal compression of the spinal cord or nerve roots. These cysts can result from an outpouching of the synovium (i.e., syno-

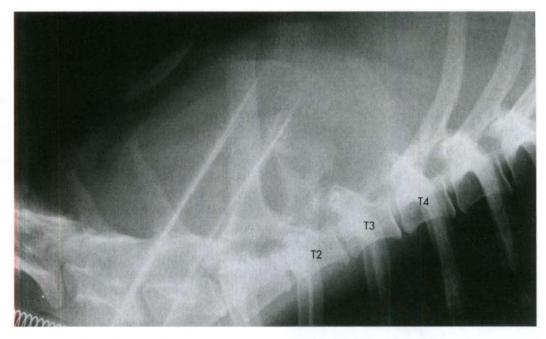


FIG 70-16

Lateral spinal radiograph from a 2-year-old Irish Setter with a 1-week history of progressive ataxia and a 12-hour history of upper motor neuron (UMN) paralysis of the rear limbs and Schiff-Sherrington syndrome. The entire spinous process of T3, the roof of T3, and most of the spinous process of T2 are destroyed, most consistent with a neoplastic process. An undifferentiated sarcoma at this site was identified on postmortem examination.



FIG 70-17

**A,** A 2-year-old cat with a 5-day course of progressive rear limb ataxia and upper motor neuron (UMN) paresis. **B,** Cerebrospinal fluid (CSF) analysis revealed an increased cell count consisting predominantly of neoplastic lymphoid cells.

vial cysts), or they may arise from mucinous degeneration of periarticular connective tissue (i.e., ganglion cysts). Synovial cysts and ganglion cysts are clinically indistinguishable, and both arise secondary to degenerative changes in the facetal joints. Degenerative changes occur because of congenital malformations, vertebral instability, or trauma. Signs are referable to the site and degree of resulting spinal cord or nerve root compression. Young giant breeds of dogs such as Mastiffs and Great Danes most commonly develop single or multiple cysts in the cervical region, which cause a UMN

myelopathy and occasionally cervical pain. Older dogs, particularly German Shepherd Dogs, have been identified with thoracolumbar or lumbosacral articular cysts that cause spinal cord or cauda equina compression. Radiographs reveal degenerative changes of the articular facets. CSF analysis reveals normal cytology and slightly increased protein consistent with a noninflammatory chronic compressive myelopathy. Myelography reveals focal extradural dorsolateral compression of the spinal cord. MRI is necessary to identify the facetal joints as the origin of the cysts and to

precisely localize the cysts before surgical therapy. Treatment consists of spinal cord decompression, cyst drainage, and arthrodesis of the facetal joint and usually produces excellent results. A similar syndrome with degeneration and bony proliferation of multiple thoracolumbar articular facets causing spinal cord compression has been reported as a hereditary condition in 4- to 10-month-old Shiloh Shepherds.

# **Arachnoid Cysts**

Focal accumulations of CSF within cystlike structures within the subarachnoid space can lead to slowly progressive, non-painful spinal cord compression in young dogs (Fig. 70-18). The cystlike structures containing CSF may represent a congenital diverticulum or a pocket caused by adhesions in the subarachnoid space secondary to trauma or disk extrusion. The cervical region and the caudal thoracic region are most often affected, and as CSF fills the arachnoid cyst, compression of the spinal cord occurs. Young large-breed dogs are most likely to be affected, with Rottweilers overrepresented. Cats are rarely affected. Myelography or MRI reveals the accumulation of CSF at the site. Exploration and marsupialization of the cyst is associated with a good prognosis for recovery if performed within 4 months of development of clinical signs and if neurologic deficits are not severe.

# Type II Intervertebral Disk Disease

Fibroid degeneration of the intervertebral disk occurs in some dogs as part of the aging process, and this can lead to prolapse of a small amount of disk nucleus into the annulus fibrosus. A fibrotic reaction ensues, resulting in a round, domelike dorsal bulging of the annulus so that it protrudes into the spinal canal and causes slowly progressive spinal cord compression (see Fig. 70-5). This type of disk pro-

trusion (i.e., Hansen's type II) is seen most commonly in aging large-breed nonchondrodystrophoid dogs, particularly German Shepherd Dogs, Labrador Retrievers, and Doberman Pinschers; however, it has also been recognized occasionally in small-breed dogs.

#### **Clinical Features**

Clinical signs result primarily from slowly progressive spinal cord compression, although spinal discomfort is apparent in a few dogs. Thoracolumbar type II disk protrusion results in UMN signs to the rear limbs, with normal forelimbs. Cervical type II disk disease may be seen in Doberman Pinschers, particularly in association with the cervical vertebral malformation-malarticulation syndrome (i.e., wobbler syndrome). In these dogs thoracic and pelvic limbs are affected, with UMN neurologic signs most prominent in the pelvic limbs.

# **Diagnosis**

Slowly progressive signs of spinal cord dysfunction in an older dog should prompt consideration of type II disk protrusion, degenerative myelopathy (DM), and neoplasia. Neurologic examination localizes the lesion to a spinal cord region, but because the site is not usually painful, spinal palpation rarely results in more precise localization. Survey radiographs of the spine are normal in most affected dogs. Disk space narrowing, osteophyte production, and end-plate sclerosis may be seen at the site of type II disk protrusion in some dogs, but these abnormalities are common at multiple sites in older large-breed dogs; thus they are not very helpful in further localizing the lesion. Myelography or advanced imaging technique (i.e., CT, MRI) is necessary to determine the extent and location of the lesion and to distinguish type II disk protrusion from spinal neoplasia and DM.

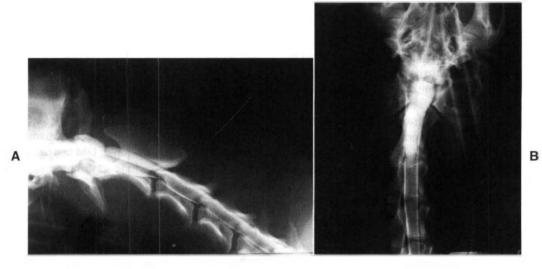


FIG 70-18

Lateral (A) and ventrodorsal (B) views of a myelogram from a 10-month-old Akita with progressive hypermetria of all four limbs and mild paraparesis. A well-defined, bulbous dilation of the dorsal subarachnoid space communicating with the rest of the subarachnoid space was present at C2-C3, suggesting an arachnoid cyst. Surgical exploration and marsupialization resulted in rapid and persistent (>6 years) return to normal gait.

#### **Treatment**

Medical therapy with antiinflammatory drugs (nonsteroidal antiinflammatory drugs or low-dose prednisone) and muscle relaxants will provide relief in dogs that are uncomfortable when the affected site is palpated or manipulated. Neurologic signs will progress, however, and surgery is recommended as the definitive treatment. Ventral decompression is performed if the cervical vertebrae are affected, whereas hemilaminectomy for decompression at the site is usually attempted for type II disks in the thoracolumbar spine. Effective surgical decompression is often difficult to achieve because of the chronic nature of the lesion and the difficulty encountered in removal of the dorsal annulus. The goal of therapy is to stabilize the animal's neurologic status. The spinal cord has usually undergone considerable chronic compression before clinical signs appear; thus full recovery is rare. A few dogs experience temporary or permanent worsening of clinical signs postoperatively.

# **Degenerative Myelopathy**

A degenerative disorder of the spinal cord white matter characterized by widespread myelin and axon loss occurs most often in aging German Shepherd Dogs and the Pembroke Welsh Corgi. DM has been recognized in dogs from 5 to 14 years of age and has rarely been seen in old dogs of other large breeds, in young German Shepherd Dogs, and in cats. A DM-like disorder has also been identified in the Pembroke Welsh Corgi. The thoracic and thoracolumbar spinal cord segments are most severely affected in all affected breeds; thus the neurologic findings suggest a lesion between T3 and L3.

#### Etiology

The cause of DM is uncertain. Some have speculated that deficiencies of nutrients or vitamins are responsible for the widespread demyelination and degeneration of axons observed histologically. An inherited cause has also been proposed in the German Shepherd Dog and the Pembroke Welsh Corgi. Whatever the initiating event, DM is generally considered to be an immune-mediated neurodegenerative disease similar to multiple sclerosis in humans. Depressed cell-mediated immunity and an increase in circulating immune complexes are consistent findings in dogs with DM, and spinal cord deposition of immunoglobulin and complement has been documented in association with histologic lesions of the disease.

# **Clinical Features**

Clinically, DM results in a slowly progressive (e.g., 6 months to 2 years) UMN paraparesis and ataxia of the rear limbs. A loss of conscious proprioception results in knuckling of the toes, wearing of the dorsal nail surfaces of the digits of the rear limbs, and severe posterior ataxia.

Increased muscle tone and hyperactivity of the rear limb tendon reflexes result in clinical localization of the problem to the spinal cord between the T3 and L3 spinal cord segments. Thoracic limbs are normal, and urinary and fecal continence are maintained until very late in the course of the disease. Neurologic deficits may be asymmetric. In a very small number of cases (<10%) a decrease or loss of pelvic limb reflexes is observed late in the course of the disease as a result of involvement of the dorsal spinal nerve roots important for the afferent arm of the reflexes.

# **Diagnosis**

A diagnosis of DM is suspected in any large-breed dog with slowly progressive UMN paresis in the rear limbs. Rear limb ataxia, a long-strided gait, toe scuffing, abnormal postural reactions (especially knuckling), and normal to increased rear limb reflexes are the most common findings. Affected dogs are systemically normal, with no site of localizable spinal pain. Neurologic findings distinguish DM from lumbosacral disease and from orthopedic disorders such as hip dysplasia and bilateral anterior cruciate ligament rupture. The primary differential diagnoses for chronic UMN paresis in the rear limbs include DM, spinal cord neoplasia, and type II disk disease.

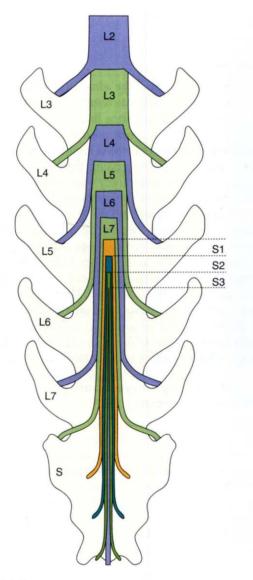
The antemortem diagnosis of DM is one of exclusion. Radiographs of the spine are normal, as is CSF analysis, although a slight increase in CSF protein concentration is occasionally found. Myelography or MRI must be performed to rule out the presence of spinal cord compression or focal spinal cord neoplasia. Normal spinal radiographs, a cytologically normal CSF, and normal spinal cord imaging in an older dog with slowly progressive UMN signs to the pelvic limbs warrant a diagnosis of DM.

# **Treatment**

No treatment has been proven effective in dogs with DM. Corticosteroids should not be administered because they cause muscle wasting and exacerbation of muscle weakness. Other immunosuppressive agents have not been shown to be beneficial. Some investigators have advocated vitamin (i.e., vitamin E, vitamin B complex, vitamin C) and omega-3 fatty acid supplementation, but conclusive evidence of their benefit is lacking. Exercise may be helpful in slowing the progression of the disease. Walking, running, and swimming for 30 minutes every other day is recommended. Some clinicians report success after long-term administration of aminocaproic acid (EACA; Amicar; Lederle Laboratories, American Cyanamide), 500 mg orally q8h. This drug blocks the final common pathway of tissue inflammation and may slow or halt the progression of DM in a few cases. Drawbacks of EACA therapy include gastrointestinal irritation, high cost, and a need to treat for 2 to 3 months before response to treatment is detectable. Administration of EACA in combination with the potent antioxidant acetylcysteine (25 mg/kg administered as a 5% solution orally q8h for 14 days, then every other day) has also been recommended. In the absence of other effective treatments for DM, these unproven treatments should be considered.

#### Cauda Equina Syndrome

In dogs the last three lumbar spinal cord segments (L5, L6, L7) are within the fourth lumbar vertebra, the sacral seg-



# FIG 70-19

The anatomy of the cauda equina region in the dog. L5-L7 spinal cord segments sit within the L4 vertebra. S1-S3 spinal cord segments are within the L5 vertebra, and the coccygeal segments are within L6. Nerve roots from all of the lumbar, sacral, and coccygeal spinal cord segments leave the canal through the intervertebral foramen just caudal to the vertebra with the same number so that these nerve roots course a considerable distance within the vertebral canal.

ments (S1, S2, S3) are within the body of the fifth lumbar vertebra, and the coccygeal segments are within the sixth lumbar vertebra. Nerve roots from these lumbar, sacral, and coccygeal segments of the spinal cord exit the spinal canal through the intervertebral foramina caudal to the vertebrae with the same number; thus they must course a considerable distance within the vertebral canal caudal to the point of termination of the spinal cord (Fig. 70-19). This collection of nerve roots descending in the vertebral canal is termed the *cauda equina*. The spinal nerves from the sacral and caudal segments overlie the lumbosacral junction, so com-

pressive diseases of this region are likely to involve the L7, sacral, and caudal nerves.

Compression of the nerves of the cauda equina (cauda equina syndrome) is usually the result of acquired type II disk protrusion at the L7/S1 intervertebral space together with progressive proliferation of joint capsules and ligaments at that site, perhaps caused by excessive motion or instability. This disorder is most common in large-breed dogs, including German Shepherd Dogs, Labrador Retrievers, and Belgian Malinoises, and particularly affects male working dogs over the age of 5 years. Rarely, compression of the cauda equina may be caused by tumor, diskospondylitis, vertebral or sacral osteochondrosis, or congenital bony malformations.

Genetic predisposition, conformation, and physical activity are all factors proposed to cause increased mechanical stress on the intervertebral disk at the lumbosacral junction, promoting type II disk prolapse at this site. Loss of the structural strength of the disk worsens instability at the site, resulting in proliferative changes in the articular facets, joint capsules, and the interarcuate ligament (i.e., ligamentum flavum). Proliferative changes result in further narrowing of the vertebral canal, compression of the cauda equina, and compression of the nerve roots as they exit the foramina (degenerative lumbosacral stenosis).

#### **Clinical Features**

Compression of the cauda equina results in a very characteristic constellation of clinical signs. Affected dogs are slow to rise from a prone position and reluctant to run, sit up, jump, or climb stairs. Rear limb lameness worsens with exercise as the blood vessels accompanying the spinal nerve roots within the already crowded intervertebral foramen dilate and further compress the nerve roots (i.e., neurogenic claudication). Affected dogs may be reluctant to raise or wag their tails.

The most consistent physical examination finding is pain elicited by deep palpation of the dorsal sacrum or by dorsiflexion of the tail or hyperextension of the lumbosacral region (Fig. 70-20). Most dogs have no neurologic deficits at the time of initial evaluation, making it difficult to distinguish affected dogs from those with pain and lameness caused by diskospondylitis, prostatic disease, or degenerative joint disease. When lumbosacral spinal canal and foraminal narrowing progress to cause compression of the L7, sacral, and caudal spinal nerves, rear limb weakness, atrophy of the muscles of the caudal thigh and distal limb, and reduced or absent hock flexion during the withdrawal reflex will become apparent. The patellar reflex may appear increased in some dogs because there is a loss of tone in the opposing caudal thigh muscles (pseudohyperreflexia). In severely affected dogs decreased anal tone and fecal and urinary incontinence will occur. Hyperesthesia or paresthesia of the perineum may develop, with self-inflicted moist dermatitis of the perineum and tail base.

# Diagnosis

Historical, physical, and neurologic examination findings are the primary basis for reaching a tentative diagnosis of cauda

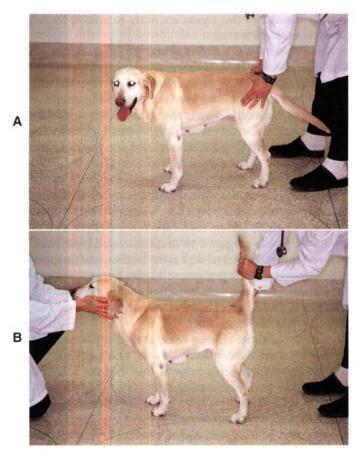


FIG 70-20
Dogs affected by cauda equina syndrome will often experience pain upon (A) deep palpation of the dorsal sacrum and (B) dorsiflexion of the tail.

equina syndrome in affected dogs. Spinal survey radiographs are useful to rule out unusual causes of lumbosacral pain (e.g., diskospondylitis, lytic vertebral neoplasia, fracture/luxation). Radiographs of this region in dogs with cauda equina syndrome may be normal or may reveal end plate sclerosis and spondylosis of the L7 and S1 vertebral end plates and narrowing or collapse of the L7-S1 intervertebral disk space. These same abnormalities are common in clinically normal dogs.

Diagnosis is based on documentation of nerve compression using imaging. Myelography (cervical injection) can document cauda equina compression, but it will not be diagnostic in those dogs (20%) in which the dural sac ends cranial to the lumbosacral junction or in dogs in which the primary lesion is lateral compression of the spinal nerves at the intervertebral foramen. When available, MRI with the spine in extension provides the most sensitive, accurate, and noninvasive means of evaluating the lumbosacral region, allowing visualization of all components potentially involved in cauda equina compression (see Fig. 70-21). There is some concern that routine use of MRI for diagnosis may lead to overinterpretation of incidental minor compressive lesions of the cauda equina; therefore clinical findings must support the MRI diagnosis. When available, electrophysiological

studies can be useful to confirm LMN disease and nerve root dysfunction of the rear limbs and tail.

#### **Treatment**

Restriction of exercise and the administration of analgesics or antiinflammatory drugs may result in temporary improvement in dogs with clinical signs limited to pain and lameness. Signs usually recur when normal activity is resumed. More definitive treatment involves lumbosacral dorsal laminectomy, excision of compressing tissues, and foraminal decompression by foraminotomy when necessary. Decompressive surgery together with lumbosacral distraction and stabilization have been recommended for dogs with marked neurologic deficits or severe pain. Descriptions of the surgical procedures are provided in Suggested Readings. Rapid relief from pain occurs in most dogs. Strict confinement is important for 4 to 8 weeks postoperatively, followed by a gradual return to exercise and work. The prognosis is excellent for resolution of lameness and mild neurologic deficits. Most dogs with mild to moderate deficits will return to working function. Dogs with severe LMN deficits or incontinence are likely to have permanent deficits.

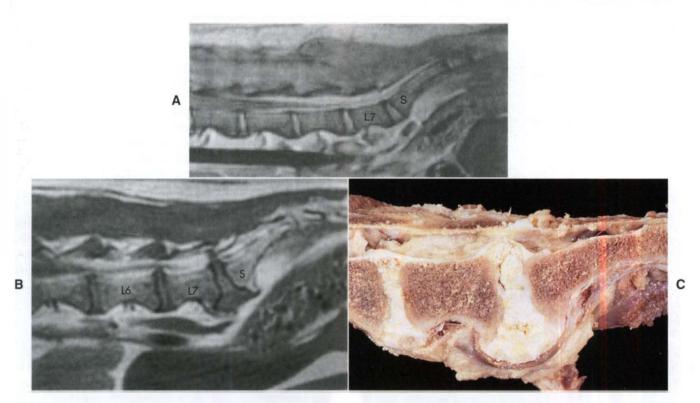
# Cervical Spondylomyelopathy (Wobbler Syndrome)

Cervical spondylomyelopathy (CSM), or canine wobbler syndrome, is a term used to describe caudal cervical spinal cord and nerve root compression in large-breed dogs that occurs secondary to developmental malformations, instability, or instability-associated changes in the spinal canal. Vertebral canal narrowing can be the result of malformed vertebral laminae, hypertrophy of the ligamentum flavum, articular facet enlargement, periarticular soft tissue hypertrophy, or a combination of these. In addition, changes in the vertebral body and end plates can result in instability that leads to intervertebral disk failure and the development of type II disk protrusions or occasionally type I disk herniation.

Typically, Great Danes and Doberman Pinschers are affected, but the condition has been reported in many large breeds of dogs. Males may be affected more often than females. Age at presentation varies from 7 weeks to 10 years. Stenosis of the cranial aspect of the cervical vertebrae (usually C4, C5, or C6) and articular facet deformities are the most common abnormalities in young Great Danes. Vertebral column instability with spinal cord compression by secondary soft tissue hypertrophy or disk, with or without congenital cervical vertebral malformation and canal stenosis (usually C5, C6, or C7), is more commonly recognized in middle-aged and older Doberman Pinschers. Genetic predisposition, overnutrition, and conformation have all been implicated in the development of this disorder.

#### **Clinical Features**

A slowly progressive course of paresis and an incoordinated or wobbling gait, particularly in the pelvic limbs, is characteristic of CSM. Affected dogs have a broad-based rear limb

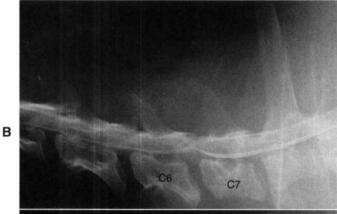


A, Normal midline sagittal T1 on a magnetic resonance image (MRI) scan of the lumbar spine of a dog. (The image reveals the high signal intensity [white] of the nucleus pulposus and the epidural fat, in contrast to the lesser signal density of the spinal cord and the nerve roots of the cauda equina [darker].) **B,** MRI from a dog with lumbosacral pain showing T1-weighted midline sagittal, displacement of epidural fat, and ventral and dorsal compression of the nerve roots at the L7-S1 disk space. Spondylosis deformans ventral to the L7-S1 intervertebral disk space and disk protrusion at the L6-L7 space can also be seen. C, Postmortem dissection of the lumbosacral region of a German Shepherd Dog with acquired degenerative lumbosacral stenosis and type II disk protrusion. The vertebral canal is compromised at the lumbosacral junction, resulting in compression of the nerves of the cauda equina. (A and B, Courtesy Dr. Greg Daniel, University of Tennessee.)

stance, ataxia, and abnormal postural reactions in the rear limbs (which are invariably more severely affected than the forelimbs). Neurologic findings in the forelimbs vary depending on whether spinal cord compression is centered in the cranial cervical region or in the caudal cervical region. Dogs with C1-C5 compression often have a floating or hypermetric front limb gait. Dogs with caudal cervical lesions may have a short-strided, weak front limb gait with a weak withdrawal reflex and pronounced atrophy of the supraspinatus and infraspinatus muscles over the scapula. Lameness and muscle atrophy in one thoracic limb or pain when traction is applied to a limb (i.e., root signature; see Fig. 70-6) suggests that nerve root compression is present. Slowly progressive deterioration in neurologic status is common, but occasionally a traumatic episode or an acute disk extrusion results in sudden tetraplegia. At the time of examination, neurologic deficits can be localized to the cervical spinal cord. Resistance to dorsal extension of the cervical spine is common, but overt cervical pain is rare unless secondary disk prolapse has occurred.

# Diagnosis

The diagnosis is suspected on the basis of signalment, history, and clinical findings. Survey radiographs are useful to rule out other disorders associated with cervical spinal cord compression but are not definitive for CSM. Severe articular facet changes or vertebral body malformations should, however, raise the index of suspicion for CSM in a largebreed dog (Fig. 70-22A). Myelography is the standard means of confirming a diagnosis of CSM and has the advantage that the spinal cord compression can be observed with the spine in multiple positions, allowing differentiation between static, dynamic, and positional lesions. CSF should be evaluated before injection of contrast. Once contrast is injected, it should be concentrated in the cervical region through patient positioning and routine lateral, ventrodorsal, dorsoventral, and then lateral flexion and traction views should be taken. Compressive lesions that improve with traction (traction-responsive or dynamic lesions), include type II disks and ligamentous hypertrophy. Spinal cord compression by bone proliferation or by extruded nucleus pulposus





#### FIG 70-22

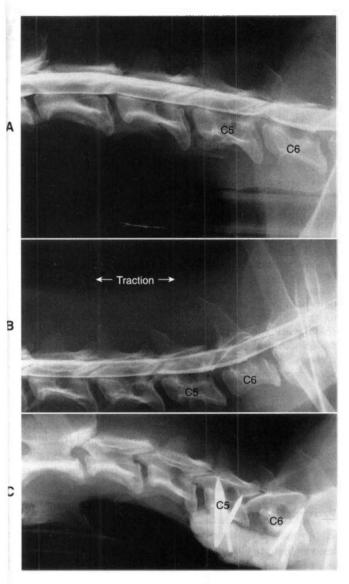
**A,** Radiographs of the cervical region in a 6-year-old Doberman Pinscher "wobbler" with a sudden onset of ataxia, paraparesis, proprioceptive deficits and hyperreflexia in the rear limbs, and mild cervical pain. A slight narrowing of the C6-C7 disk space can be seen; the vertebral canal is stenotic within the cranial aspect of C6 and C7. **B,** Myelography shows spinal cord compression by a ventral extradural mass at C6-C7 that is not altered significantly with traction, **(C).** Surgery revealed a large amount of disk material within the vertebral canal at this **site**.

(type 1 disk) will not resolve with traction (traction nonresponsive or static lesions; Fig. 70-22, B and C). Some dogs have spinal cord compression that is not evident in neutral or traction views but that becomes apparent with flexion or extension (positional lesions). Ideally, all conventional myelograms for CSM should be followed by a CT scan or MRI to improve surgical planning. Rational decisions regarding therapy and prognosis can be made after determining whether compression is at one site or many, is primarily dorsal or ventral, and is static or dynamic. Because a temporary worsening of neurologic status may occur after imaging dogs with CSM under general anesthesia, if surgery is planned, it should be scheduled 48 to 72 hours after imaging to allow recovery and neurologic stabilization. All affected animals should be evaluated for systemic disease before surgery, particularly Doberman Pinschers that may have concurrent hypothyroidism, von Willebrand's disease, or cardiomyopathy.

#### **Treatment**

The clinical course of untreated wobbler syndrome is chronically progressive. Medical or surgical therapy can be used to attempt to relieve clinical signs. Severe exercise restriction, use of a harness, and administration of antiinflammatory doses of prednisone may result in temporary improvement in neurologic function. Sometimes, long-term management of dogs with minimal or mild signs of neurologic dysfunction is satisfactory with exercise restriction and corticosteroid therapy alone (prednisone 0.5 mg/kg orally q12h for 2 days; then 0.5 mg/kg once every day for 2 days; then 0.5 mg/kg once every other day for 14 days; then 0.25 mg/kg once every other day for 2 months).

Although initial improvement is common after medical therapy, the underlying compression and instability persist and generally progress without more definitive treatment. Surgical treatment is recommended in all dogs with persistent neurologic deficits. The main factor determining the specific surgical procedure to be recommended is the appearance of the cord myelographically, especially on the traction view. If the only lesion identified is static (traction nonresponsive) ventral spinal cord compression resulting from type 1 disk herniation, then ventral decompression is performed. If a single dynamic lesion is causing compression, such as a bulging annulus (ventrally) or a hypertrophied ligamentum flavum (dorsally), then a distraction/fusion technique is used to pull the vertebral bodies apart and maintain the separation, decreasing spinal cord compression and relieving pressure on the nerve roots (Fig. 70-23). The method used depends on the number of sites involved and surgeon preference. If the imaging studies indicate static dorsal compression of the spinal cord resulting from vertebral malformation or articular process osteophytes, then a dorsal decompressive technique must be attempted. Details of the surgical procedures and potential complications are discussed in Suggested Readings.



#### FIG 70-23

A, Cervical myelogram of an 11-year-old Doberman/
Weimaraner cross with a chronic history of nonpainful
ataxia and hypermetria of all four limbs. Narrowing of the
C5-C6 disk space and thinning of the dorsal contrast
column over this site (in association with dorsal deviation
and thinning of the ventral contrast column) can be seen.
B, The dramatic resolution of this spinal cord compression
in the traction view suggests a dynamic compression by a
bulging annulus fibrosus or ligamentum flavum. C, Surgery
was performed to maintain traction on the spine at this site.

# **Prognosis**

Dogs with wobbler syndrome have extremely variable prognoses, depending on their neurologic status, the temporal course of their disease, and the specific abnormalities that are present. Surgical results in ambulatory animals with a short history and only one lesion can be good, with up to 80% success reported. Multiple lesions, chronic disease, and an inability to walk are all associated with a poor prognosis.

# PROGRESSIVE DISORDERS IN YOUNG ANIMALS Breed-Associated Neuronal Abiotrophies and Degenerations

Neuronal abiotrophies and degenerative disorders have been recognized in many breeds of dogs. Progressive neurologic dysfunction usually begins early in life. In disorders affecting the entire spinal cord, clinical signs involving the rear limbs are often noted early in the course of disease with progression to tetraparesis. Disorders that primarily affect white matter and result in UMN signs are most often seen in Rottweilers, Afghan Hounds, Dalmatians, and Jack Russell Terriers. Disorders primarily affecting gray matter and causing LMN signs are seen in Alaskan Malamutes, Boxers, Brittany Spaniels, German Shepherd Dogs, English Pointers, and Maine Coon Cats. The disorders are diagnosed on the basis of the typical clinical course, the signalment, and the lack of any definable etiology on screening blood tests, spinal radiographs, CSF analysis, myelography, and other diagnostic testing. Diagnosis is confirmed by necropsy examination in most cases. No treatment is available.

# **Metabolic Storage Diseases**

A large group of rare disorders, characterized pathologically by the accumulation of metabolic products in cells caused by a genetically based enzyme deficiency, may result in signs of spinal cord dysfunction. The enzyme deficiency itself or the accumulation of the metabolic intermediates within cells causes a gradual progression of neurologic signs. Spinal signs are usually UMN in nature, although peripheral nerve dysfunction may occur. Cortical signs (e.g., seizures) and cerebellar signs (e.g., hypermetria) are more common. Signs are gradually progressive and usually obvious within the first year or two of life. Metabolic storage diseases are diagnosed on the basis of the typical clinical course and signalment; the lack of any other identifiable etiology; and, in some cases, organomegaly, abnormal appearance, blindness, and other readily identifiable clinical abnormalities resulting from the accumulation of metabolic product in extraneural sites.

# **Atlantoaxial Instability and Luxation**

Normally, the atlas (C1) and the axis (C2) are bound together by ligaments. The dens, a bony projection from the cranial aspect of the body of the axis, is held firmly against the floor of the atlas by the transverse ligament, maintaining alignment of these two vertebrae and integrity of the spinal canal. Malformation or absence of the dens leading to instability can be seen as a congenital defect in many small breeds of dogs, including the Yorkshire Terrier, Miniature or Toy Poodle, Chihuahua, Pomeranian, and Pekingese; it occurs rarely in large-breed dogs and in cats. The malformation and resultant atlantoaxial instability lead to repeated spinal cord trauma and slowly progressive signs of cranial cervical spinal cord compression. Alternatively, in young dogs with congenital atlantoaxial instability, mild trauma may cause C1/C2 luxation, precipitating a sudden onset of cervical pain,

tetraparesis, or paralysis. Of course, in any normal dog severe trauma could result in traumatic luxation or fracture in this region with similar clinical findings.

#### **Clinical Features**

Dogs with congenital atlantoaxial instability typically develop UMN signs indicating cervical spinal cord compression before 2 years of age. Clinical signs include neck pain (30% to 60%), low head carriage, ataxia, tetraparesis and postural reaction and conscious proprioceptive deficits in all limbs. Manipulation of the spine should be avoided because it can exacerbate motor dysfunction. Paralysis is rare, but if it does occur, it may be accompanied by hypoventilation. Some dogs have a persistent head tilt or turn. Atlantoaxial luxation secondary to malformation should be suspected in any young (i.e., 6- to 18-month-old) toy-breed dog with a history of cervical pain, tetraparesis, or tetraplegia. Atlantoaxial luxation should also be considered as a possible differential diagnosis in any dog with evidence for high cervical spinal cord disease (UMN tetraplegia) after trauma.

## Diagnosis

Radiographic examination should be performed initially without anesthesia when atlantoaxial luxation is suspected to prevent inadvertent overflexion or twisting of an unstable cervical spine. Lateral and oblique lateral views may aid in demonstrating absence or deformity of the dens. Accurate positioning with the region of interest located in the center of the film is important. Instability with significant luxation can be recognized on a lateral view as widening of the space between the dorsal arch of the atlas and the dorsal spinous process of the axis on the lateral view and dorsal displacement of the body of the axis (Fig. 70-24). In cases of congenital luxation the dens may be recognized as abnormal, and fracture of the dens may be apparent in traumatic luxations. If preliminary radiographs are not diagnostic, the animal should be anesthetized and the radiographs repeated with the head gently flexed. This may allow demonstration of the instability. Extreme care is critical when manipulating an animal suspected of having atlantoaxial instability under anesthesia because rotation or excessive flexion of the neck may result in further spinal cord compression, respiratory paralysis, and death. Splinting the animal's head and neck in extension before anesthesia is recommended to prevent excessive flexion during induction of anesthesia and intubation.

#### **Treatment**

Treatment for acute severe tetraparesis caused by atlantoaxial luxation should include medical treatment as for acute spinal cord trauma (see Fig. 70-4). Nonsurgical treatment should include cage rest, application of a neck brace, and administration of analgesics. The purpose of the splint is to immobilize the atlantoaxial junction, so the splint must extend from over the head cranial to the ears and go back to the chest. Nonsurgical treatment is recommended in small dogs that fracture a normal atlantoaxial articulation. It is



FIG 70-24

Atlantoaxial subluxation in a 7-month-old Bichon Frise. The dens rises well above its normal position, consistent with rupture of its ligament and compression of the cervical spinal cord. The space between the arch of the atlas and the spinous process of the axis is increased. This dog had a chronic history of intermittent cervical pain and severe upper motor neuron (UMN) tetraparesis.

also very effective short term in dogs with congenital lesions, but the long-term results are unknown. Surgical treatment is effective but may be associated with high perioperative morbidity and mortality. Dorsal and ventral techniques are described in Suggested Readings.

#### **Prognosis**

The prognosis for recovery is good in dogs with congenital lesions that survive the perioperative period. Outcome is most likely to be positive if the onset of signs occurs before the patient is 2 years of age, when signs have been present for less than 10 months, and if surgical reduction is good.

# NONPROGRESSIVE DISORDERS IN YOUNG ANIMALS Spina Bifida

Spina bifida results from embryonic failure of fusion of the two halves of the dorsal spinous processes of the vertebral arch. Although spina bifida may occur anywhere along the spinal canal, the caudal lumbar and lumbosacral region is most often affected. This malformation is most common in English Bulldogs and Manx cats. In the Manx cat the condition is an autosomal recessive trait and may be associated with caudal agenesis. Clinical signs are nonprogressive and present from birth, including rear limb LMN paresis, fecal and urinary incontinence, loss of perineal sensation, and decreased tone of the anal sphincter. No therapy is available.

# Caudal Agenesis of Manx Cats

Congenital malformations of the sacrococcygeal spinal cord and vertebrae are common in tailless Manx cats. Clinical signs result from agenesis or dysgenesis of the caudal vertebrae and sacral spinal cord. Signs are typically present from birth and include hopping or crouched pelvic limb gait, fecal and urinary incontinence, and chronic constipation.

## Spinal Dysraphism

Spinal dysraphism is an inherited congenital malformation of the spinal cord. It results from the abnormal development of the structures of the spinal cord along the central plane. The malformation includes a dilated or absent central canal, cavitation in the white matter, and the abnormal presence of ventral gray column cells across the median plane between the central canal and the ventral median fissure. Spinal dysraphism is recognized most commonly in Weimaraners, although other breeds are occasionally affected.

Clinical signs are present at birth. Affected dogs have a symmetric, bunny-hopping pelvic limb gait; a wide-based stance; and depressed proprioception. The patellar reflex is normal. The pelvic limb flexor reflex stimulated in one limb usually elicits simultaneous flexion of both pelvic limbs. Clinical signs caused by spinal dysraphism do not progress, and mildly affected dogs can live a normal life.

# Syringomyelia/Hydromyelia

Cystic accumulations of fluid within the spinal cord causing compression of adjacent parenchyma are being recognized with increasing frequency as advanced diagnostic imaging techniques (i.e., CT, MRI) are used for neurologic diagnosis. Syringomyelia is the development of a CSF-filled cavity anywhere within the cord, and hydromyelia is the accumulation of excessive CSF within a dilated central canal. These disorders can develop as a result of altered CSF pressures within the spinal canal, a loss of spinal cord parenchyma, or secondarily to obstructed CSF flow caused by congenital malformations or inflammatory or neoplastic disorders.

Clinical signs reflect the site and degree of spinal cord parenchymal destruction. Ataxia and paresis are common. With cervical lesions UMN signs are more pronounced in the rear limbs if the dorsal and lateral portions of the cord are affected. When the spinal cord damage is more centrally located, ataxia and paresis will often be more significant in the forelimbs than in the rear limbs (i.e., central cord syndrome). Spinal pain may be seen because of stretching of nerve roots or meninges. Scoliosis occasionally develops as LMN cell body damage within the cord causes asymmetric denervation of the paraspinal muscles, resulting in vertebral deviation. Syringohydromyelia has been reported in numerous Cavalier King Charles Spaniels with occipital bone malformations leading to overcrowding at the foramen magnum.

The onset of clinical signs in this breed is usually in young adult dogs, with most dogs presenting because of scratching at the shoulder region; intolerance to touching of the ear, limb, or neck of the affected side; and cervical pain. Muscle atrophy and LMN weakness of the associated thoracic limb and ataxia and UMN deficits of the rear limbs may also be seen. Diagnosis is most reliably made with MRI. Treatment with antiinflammatory doses of prednisone to decrease CSF production may result in clinical improvement. Decompression of the caudal fossa with an occipital craniectomy to reestablish normal CSF flow can be effective.

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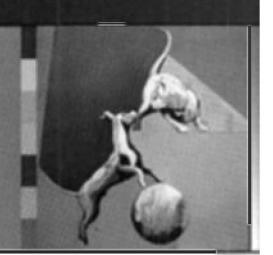
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# CHAPTER

# Disorders of Peripheral Nerves and the Neuromuscular Junction



# CHAPTER OUTLINE

# GENERAL CONSIDERATIONS FOCAL NEUROPATHIES

Traumatic Neuropathies
Peripheral Nerve Sheath Tumors
Facial Nerve Paralysis
Trigeminal Nerve Paralysis
Hyperchylomicronemia
Ischemic Neuromyopathy

# POLYNEUROPATHIÉS

Congenital/Inherited Polyneuropathies
Acquired Chronic Polyneuropathies
Acquired Acute Polyneuropathies
DISORDERS OF THE NEUROMUSCULAR JUNCTION

Tick Paralysis
Botulism
Myasthenia Gravis
DYSAUTONOMIA

#### GENERAL CONSIDERATIONS

The clinically important peripheral nerves are the peripheral nerves arising from the spinal nerves in the cervical and lumbar intumescences to innervate the muscles of the limbs and the 12 pairs of cranial nerves originating in the brainstem. Spinal nerve or peripheral nerve lesions result in lower motor neuron (LMN) motor signs of weakness, decreased tone, and decreased reflexes in affected muscles and limbs. When sensory components of the peripheral nerves are involved, there may also be decreased, absent, or altered sensation in the skin supplied by that nerve.

At the neuromuscular junction (NMJ) a nerve impulse reaching the nerve terminal initiates the release of acetylcholine (ACh) into the synaptic cleft. ACh binds to ACh receptors on the postsynaptic (muscle) membrane, inducing a conformational change and ion flux that results in muscular contraction. Presynaptic NMJ disorders that interfere with the release of ACh from the nerve terminal result in general-

ized LMN signs of weakness and hyporeflexia similar to disorders affecting peripheral nerves. Myasthenia gravis is a postsynaptic disorder that causes partial failure of neuromuscular transmission, resulting in weakness with normal spinal reflexes, similar to the muscle disorders discussed in Chapter 72.

## **FOCAL NEUROPATHIES**

# TRAUMATIC NEUROPATHIES

Traumatic neuropathies are common. They result from mechanical blows, fractures, pressure, stretching, laceration, and the injection of agents into or adjacent to the nerve. Diagnosis is usually straightforward and is based on the history and clinical findings. Individual nerves or a group of adjacent nerves may be damaged. Traumatic radial nerve paralysis, complete avulsion of the entire brachial plexus, and sciatic nerve injury are most common in the dog and cat (Table 71-1; Fig. 71-1).

Electrodiagnostic testing, when available, can be used to evaluate the extent of nerve damage. In 5 to 7 days after denervation of a muscle, electromyography detects denervation action potentials (i.e., increased insertional activity and spontaneous action potentials) in the muscles normally supplied by the damaged nerve (see Table 71-1). Nerve conduction studies proximal and distal to the site of injury are also useful in assessing nerve integrity.

When an animal is presented with a peripheral nerve injury, careful mapping and assessment of cutaneous sensation and motor function help determine the precise location of the injury, and sequential mapping can be used to monitor progress (Fig. 71-2). The regenerative ability of a nerve is proportional to the continuity of connective tissue structures remaining around the damaged portion of the nerve. If adequate connective tissue scaffolding is left, axonal regeneration can occur at a rate of 1 to 4 mm/day. Severed nerve ends should be surgically brought into apposition and anastomosed to increase the likelihood of regeneration. The closer a nerve injury is to the innervated muscle, the better the chances are of recovery.



TABLE 71-1

Traumatic Neuropathies

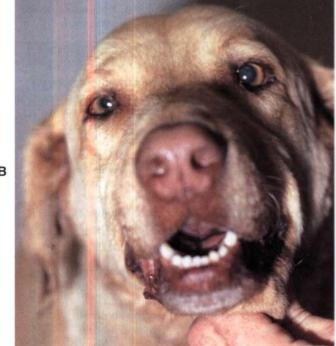
PERIPHERAL NERVES DAMAGED	MOTOR DYSFUNCTION	SKIN REGION OF SENSATION LOSS	MUSCLES AFFECTED
Lesions of Nerves of the B	rachial Plexus		
Peripheral radial nerve damage (at level of elbow)	Loss of carpus and digit extension; may walk on dorsal paw or carry limb	Cranial and lateral forearm and dorsal forepaw	Extensor carpi radialis, ulnaris lateralis, extensors
Brachial plexus avulsion (j	proximal damage)		
Suprascapular nerve ([C5]),C6,C7	Loss of shoulder extension; muscle atrophy over scapular spine	None	Supraspinatus, infraspinatus
Axillary nerve ([C6],C7,C8)	Reduced shoulder flexion. Deltoid muscle atrophy	Lateral brachium over humerus and scapula	Deltoideus, teres major, teres minor, subscapularis
Musculocutaneous (C6,C7,C8)	Reduced elbow flexion	Medial forearm	Biceps brachii, brachialis, nerve coracobrachialis
Radial nerve (C7,C8,T1,[T2])	Reduced extension of elbow, carpus, and digits; cannot support weight	Cranial and lateral forearm and foot (except digit 5)	Triceps brachii, extensor carpi radialis, ulnaris lateralis, digital extensors
Median nerve (C8T1[T2])	Reduced flexion of carpus and digits	None	Flexor carpi radialis, digital flexors
Ulnar nerve (C8T1[T2])	Reduced flexion of carpus and digits	Caudal forearm distal to elbow, 5 <sup>th</sup> digit	Flexor carpi ulnaris, deep and digital flexors
Lesions of Nerves of the L	umbosacrai Plexus		
Femoral nerve damage L4,L5,L6	Inability to extend stifle. Cannot support weight. Atrophy of quadriceps Loss of patellar reflex	Medial limb (toes to thigh)	lliopsoas, quadriceps, sartorius
Obturator nerve ([L4],L5,L6)	Abduction of limb at hip	None	External obturator, pectineus gracilis, adductor
Sciatic nerve paralysis (L6,L7,S1,[S2])	Reduced flexion and extension of hip; loss of stifle flexion; loss of hock flexion and extension; hock dropped; paw is knuckled but weight bearing does occur; absent withdrawal reflex; atrophy of cranial, tibial, semimembranosus, and semitendinosus muscles	All regions below stifle except medial surface	Biceps femoris, semimembranosus, semitendinosus
Tibial branch (L7, S1,[S2])	Dropped hock	Plantar paw and limb distal to stifle	Gastrocnemius, popliteus, digital flexors
Peroneal branch (L6,L7,S1,S2) Cranial and caudal gluteal (L7,S1,S2)	Stands knuckled; no cranial tibial reflex; weak hock flexion Reduced hip flexion; stifle rotates laterally during weight bearing	Cranial and lateral limb (distal to stifle)) None	Peroneus longus, digital extensors, cranial tibial Superficial, middle, and deep gluteals, tensor fascia lata

Physical therapy such as swimming, limb manipulation, heat therapy, and massage help delay muscle atrophy and tendon contracture and speed return of function in animals with incomplete lesions. Self-mutilation may become a problem 2 to 3 weeks after injury because regeneration of sensory nerves can result in abnormal sensation lasting 7 to 10 days. Lack of improvement in motor function after 1 month warrants consideration of amputation of the affected limb or, when feasible, arthrodesis for limb salvage.

#### PERIPHERAL NERVE SHEATH TUMORS

Tumors of nerve sheath origin arise from cells surrounding the axons in peripheral nerves or nerve roots. Most of these tumors are anaplastic with a high mitotic index and aggressive biological behavior and are therefore classified as malignant peripheral nerve sheath tumors (PNSTs) regardless of their cell of origin. These tumors are a relatively common cause of lameness and neuropathy when they involve the nerves of the brachial plexus. Lymphoma may also involve





**A,** Traumatic brachial plexus avulsion in a Chesapeake Bay Retriever. **B,** Horner's syndrome in the same dog.

the nerve roots or peripheral nerves of dogs and cats (Fig. 71-3).

#### **Clinical Features**

Clinical signs depend on tumor location and the nerves involved. Trigeminal nerve sheath tumors cause ipsilateral atrophy of the temporalis and masseter muscles. Malignant PNSTs in dogs most commonly affect the caudal cervical (C6-C8) or cranial thoracic (T1-T2) nerve roots of the brachial plexus, resulting in lameness, muscle atrophy, pain, and lifting of the affected leg (root signature). The insidious onset of these tumors may make it difficult to differentiate them from lameness caused by a vague musculoskeletal injury or nerve root compression caused by intervertebral disk disease. With progression of the tumor, atrophy, weakness, and loss of reflexes may occur as the affected peripheral



Mapping the region of sensory loss is important in localizing lesions and monitoring improvement. This dog has a caudal brachial plexus avulsion, so he has lost superficial sensation on the limb distal to the elbow.

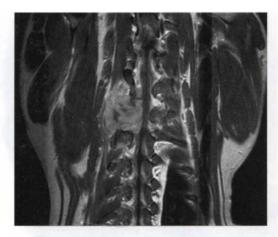


FIG 71-3
Dramatic muscle atrophy and sensory loss in a cat with lymphoma involving the L6-S1 nerve roots.

nerve is destroyed. Tumors involving the T1-T3 nerve roots commonly interrupt the sympathetic pathway and result in ipsilateral Horner's syndrome. Similarly, the ipsilateral cutaneous trunci reflex will be absent if the C8-T1 ventral nerve roots are damaged. Tumors originating in the spinal canal and extending peripherally and tumors originating in the brachial plexus and extending proximally into the vertebral canal will often cause upper motor neuron (UMN) deficits in the ipsilateral hindlimb as the tumor expands, but this may not be clinically apparent until significant spinal invasion has taken place.

#### Diagnosis

Radiographs of the spine are indicated if a neoplasm involving a spinal nerve root is suspected. Nerve sheath tumors rarely cause bony changes, although expanding tumors that pass through an intervertebral foramen may cause widening of the foramen as a result of pressure necrosis. Myelography can be useful to identify spinal cord compression.



Magnetic resonance imaging (MRI) of the spine of a dog with a nerve root tumor causing lameness, and lowor motor neuron paresis of the right forelimb reveals invasion of the tumor into the vertebral canal.

Electromyography and nerve conduction velocity determinations may confirm the presence of a peripheral nerve lesion and aid in localization. Deep palpation of the axilla under general anesthesia and ultrasound examination may reveal a mass. Advanced diagnostic imaging (i.e., computed tomography [CT], magnetic resonance imaging [MRI]), when used with contrast enhancement, is the best way to delineate tumor masses and detect vertebral canal invasion (Fig. 71-4).

# **Treatment**

The treatment of choice for a PNST is surgical removal. Aggressive removal of distally located tumors can result in a cure. Extensive neurologic damage by the tumor, damage affecting several spinal nerves or nerve roots, or severely atrophied muscles usually require amputation of the limb. Nerve root tumors that have progressed to cause spinal cord compression usually involve multiple nerve roots, are rarely completely resectable, and are associated with a poor prognosis. Postoperative irradiation may be indicated in an attempt to slow tumor recurrence.

# **FACIAL NERVE PARALYSIS**

Facial nerve (CN7) paralysis is recognized frequently in dogs and cats. In 75% of dogs and 25% of cats with acute facial nerve paralysis, there are no associated neurologic or physical abnormalities and no underlying cause can be found, prompting a diagnosis of idiopathic facial nerve paralysis. Canine hypothyroidism is occasionally associated with a mononeuropathy involving the facial nerve, but the causality is uncertain. Traumatic injury to the facial nerve can also occur at the level of the brainstem or peripherally as the nerve courses through the petrous temporal bone.

The most common identifiable cause of facial nerve paralysis, however, is damage to branches of the facial nerve within the middle ear secondary to inflammation, infection,

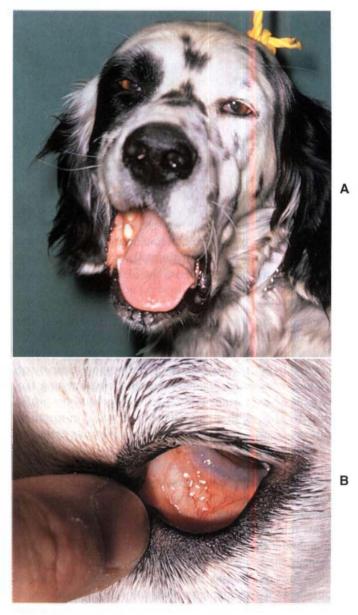


FIG 71-5
Idiopathic facial nerve paralysis in a 4-year-old English
Setter. Note the drooping lip and ear (A) and the inability
to blink (B). The paralysis resolved in 14 days without
therapy.

or neoplasia. Otitis media and otitis interna usually result from extension of bacterial otitis externa, particularly in breeds predisposed to chronic bacterial otitis externa (e.g., Cocker Spaniels, German Shepherd Dogs, and Setters. Foreign bodies (e.g., grass awns), malignant tumors (in both dogs and cats), and benign nasopharyngeal polyps (in cats) involving the middle ear can also cause facial nerve paralysis.

#### **Clinical Features**

Clinical manifestations of facial nerve paralysis include an inability to close the eyelid, move the lip, or move the ear.

Affected animals are unable to blink spontaneously or in response to visual or palpebral sensory stimulation. Corneal ulceration may occur because of an inability to distribute the tear film by blinking (neuroparalytic keratitis) and loss of facial nerve (parasympathetic)-stimulated lacrimal gland secretion (neurogenic keratitis). Drooping of the ear and lip as a result of loss of muscle tone on the affected side is common (Fig. 71-5). Many dogs and cats with facial nerve paralysis caused by middle ear disease also develop peripheral vestibular signs and/or Horner's syndrome because of the close proximity of the nerves in the area of the middle and inner ear. Rarely, a painful syndrome of hemifacial spasm with facial muscle contracture and lip retraction may occur as a result of facial nerve irritation. This should be differentiated from nonpainful muscle atrophy and contracture, which occur relatively commonly in animals with longstanding facial nerve paralysis (Fig. 71-6).

# **Diagnosis**

Idiopathic facial nerve paralysis can be diagnosed only after excluding all other causes. A complete neurologic examination should be performed to ensure that there are no other cranial nerve deficits, ataxia, or proprioceptive deficits suggesting a brainstem lesion. Clinicopathologic testing (i.e., complete blood count [CBC], serum biochemistry profile, urinalysis) is required to evaluate for systemic or metabolic disease. A suspicion of hypothyroidism warrants evaluation of thyroid function (see Chapter 51).

All dogs and cats with facial nerve paralysis should be evaluated carefully for disease of the middle and inner ear. Careful otoscopic examination is important, even if general anesthesia is required. Most animals with otitis media or otitis interna have obvious otitis externa and a tympanic membrane that appears abnormal or ruptured, but occasionally the otoscopic examination is normal. If the suspicion for middle and inner ear disease is high, general anesthesia for radiographs, advanced imaging, and myringotomy to collect a sample from the middle ear are warranted (Fig. 71-7).

#### **Treatment**

No treatment exists for idiopathic facial nerve paralysis. If keratoconjunctivitis sicca is present, the eye should be medicated as needed. The paralysis may be permanent, or spontaneous recovery may occur in 2 to 6 weeks.

If evaluation of the middle and inner ear reveals bony lysis or extensive soft tissue proliferation, this suggests that neoplasia could be the cause of facial nerve paralysis. A biopsy should be performed, and surgery to debulk or remove the tumor should be considered. The prognosis for cure with feline benign inflammatory nasopharyngeal polyps in this location is excellent. Tumors of the bulla, bony labyrinth, ear canal, or peripheral nerve are less likely to be treated effectively using surgery alone. Radiotherapy or chemotherapy may be beneficial in some cases.

Medical treatment of dogs and cats with bacterial otitis media and otitis interna is discussed in Chapter 68.

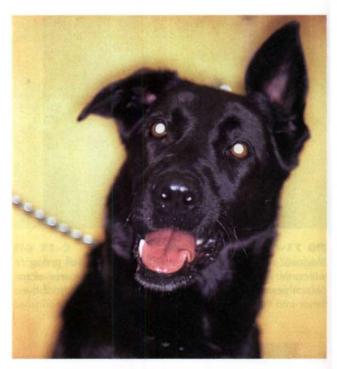


FIG 71-6
Contraction of the muscles on the left side of the face developed in an adult dog with a 2-month history of idiopathic left-sided facial nerve paralysis. Note the erect left ear and nasal deviation to the left.

#### TRIGEMINAL NERVE PARALYSIS

Bilateral motor paralysis of the trigeminal nerves results in the sudden onset of an inability to close the jaw or prehend food. The mouth hangs open, but it can be physically closed and manipulated without resistance (Fig. 71-8). Swallowing is usually normal. Severe rapid atrophy of the muscles of mastication may occur, and a few animals display concurrent Horner's syndrome. Sensory loss (trigeminal distribution) is variable, but if hyposensitization of the corneal surface occurs, there will be decreased reflex tear formation and loss of trophic factors, leading to corneal ulceration without significant discomfort (neurotrophic keratitis).

Idiopathic trigeminal paralysis is seen in middle-aged and older dogs and rarely in cats. The diagnosis relies on clinical signs and on ruling out other possible causes. Rabies and other inflammatory central nervous system (CNS) diseases are unlikely in the absence of other clinical signs. Neoplastic and traumatic disorders are not usually bilateral, although bilateral motor trigeminal nerve infiltration has been reported in a dog with multicentric lymphoma.

The etiology of this idiopathic disorder is unknown. If biopsy of the nerve is performed, it reveals bilateral nonsuppurative neuritis of all motor branches of cranial nerve 5 associated with demyelination. Treatment consists of supportive care. Most dogs can drink and maintain adequate hydration if they are given water in a deep container, such as a bucket. Hand-feeding may be necessary. Holding the mouth partially closed in a sling may facilitate eating and drinking

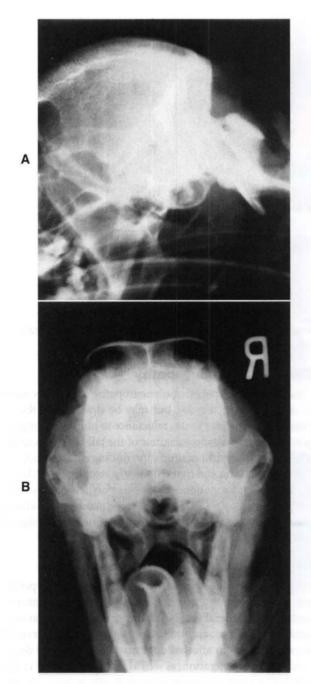


FIG 71-7
Skull radiographs of a 4-year-old Cocker Spaniel with bilateral otitis media resulting in bilateral facial nerve paralysis. Both bullae chambers are opacified, and the left bulla is thickened by irregular and slightly indistinct new bone.

during recovery (Fig. 71-9). Lubricating eye ointments may help prevent corneal ulceration. The prognosis is excellent, with most animals recovering completely within 2 to 4 weeks.

#### **HYPERCHYLOMICRONEMIA**

Peripheral neuropathies have been observed in cats of all ages with a mutation in the gene encoding lipoprotein lipase.



FIG 71-8
Idiopathic trigeminal nerve motor paralysis resulting in a dropped jaw and excessive drooling in a 9-year-old Labrador Retriever. The paralysis resolved in 14 days without therapy.

Affected cats have delayed clearance of chylomicrons from the circulation, resulting in the formation of lipid granulomas (xanthomas) in the skin and other tissues. These xanthomas may compress a nerve against bone, resulting in neuropathology. Horner's syndrome and tibial and radial nerve paralysis are most often seen. Clinicopathologic testing reveals fasting hyperchylomicronemia and blood that looks like cream-of-tomato soup. Diagnosis is by biopsy of the xanthomas or measurement of lipoprotein lipase concentration. The neurologic signs are reversible if hyperchylomicronemia can be controlled by feeding affected cats a low-fat diet (see Chapter 54).

#### ISCHEMIC NEUROMYOPATHY

Caudal aortic thromboembolism causes paralysis from ischemic damage to affected muscles and peripheral nerves. Ischemia is caused by vasoconstriction of the collateral circulation to the limbs as a result of release of thromboxane A2 and serotonin from platelets in a clot lodged in the aortic trifurcation. Caudal aortic thromboembolism is common in cats and rare in dogs. An acute onset of LMN pelvic limb paralysis or paresis is seen. Femoral pulses are weak or absent. The legs and feet are cool, and the pads are no longer pink (Fig. 71-10). Hemorrhage does not occur when a toenail is cut short on an affected foot. The affected muscles are swollen and painful. LMN paralysis with complete areflexia of the rear limbs are common, although occasionally the patellar reflex is maintained. Within hours, rigid extension of the legs may occur as a result of contracture of ischemic muscle. In cats cardiomyopathy is most common. In dogs a disorder associated with hypercoagulability can usually be identified (see Chapter 12), and the dog should be evaluated for nephrotic syndrome, hyperadrenocorticism, heartworm disease, neoplasia, and endocarditis. Treatment of feline aortic thromboembolism is discussed in Chapter 12.



FIG 71-9
The use of sling to support the jaw and hold the mouth partially closed can help dogs with idiopathic trigeminal motor paralysis to eat.

# **POLYNEUROPATHIES**

# CONGENITAL/INHERITED POLYNEUROPATHIES

A number of breed-associated degenerative peripheral neuropathies occur. They usually affect young animals and are presumed to have a hereditary basis. Most of these disorders cause progressive generalized LMN dysfunction with severe tetraparesis, muscle atrophy, and hyporeflexia. Pathologic lesions vary with each disorder but may involve the motor neurons in the ventral horn of the spinal cord, ventral nerve roots, or peripheral nerves. In Rottweilers, Dalmatians, and Great Pyrenees, concurrent laryngeal paralysis is common. Certain inherited storage diseases will cause CNS signs as well as diffuse LMN paresis. Familial sensory neuropathies causing diminished sensation /nociception and self-mutilation (English Pointers) and sometimes mild ataxia and loss of proprioception (Longhaired Dachshunds) can also occur. All of these conditions are extremely rare and are reviewed in detail in Suggested Readings. Presumptive diagnosis is by recognition of typical breed and age of onset and presentation and ruling out of other disorders. Definitive diagnosis requires electrophysiological evaluation of nerve function and nerve biopsy.

# ACQUIRED CHRONIC POLYNEUROPATHIES

Polyneuropathies affect more than one group of peripheral nerves, resulting in generalized LMN signs that include flaccid muscle weakness or paralysis, marked muscle atrophy, decreased muscle tone, and reduced or absent reflexes. Proprioceptive deficits may be evident if the sensory portions of the nerves are severely affected. Electromyography, when available, reveals evidence of denervation, and nerve conduction velocity is decreased in affected nerves. Nerve biopsies typically reveal axonal degeneration and demyelination regardless of the underlying cause, so a thorough systemic investigation of possible etiologies is required to

reach a diagnosis and recommend appropriate treatment (Box 71-1).

# **Diabetic Polyneuropathy**

Clinical signs of diabetic polyneuropathy are usually subtle or inapparent in the dog but may be dramatic in the cat. Weakness of the rear limbs, reluctance to jump, a plantigrade pelvic limb stance, and weakness of the tail are characteristic (Fig. 71-11). Physical examination findings may include rear limb hyporeflexia and marked muscle atrophy. (See Chapter 52 for more information.) If diabetic polyneuropathy is recognized early, establishing improved glucose regulation can result in stabilization or improvement of neurologic signs in some cats.

## Hypothyroid Polyneuropathy

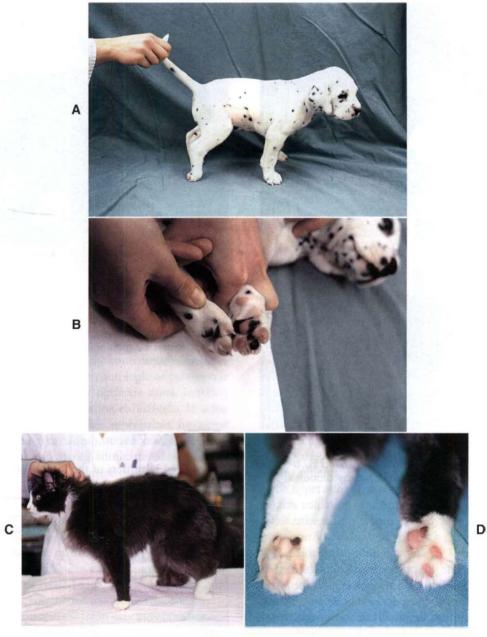
Hypothyroidism has been associated with a variety of peripheral nerve abnormalities, including diffuse LMN paralysis, unilateral peripheral vestibular disease, facial nerve paralysis, laryngeal paralysis, and megaesophagus in dogs. Nerve and muscle biopsies in affected dogs may show neuronal degeneration and regeneration, as well as muscle fiber type grouping that is most indicative of neurogenic atrophy. In some hypothyroid dogs neurologic signs resolve once supplementation with thyroid hormone is initiated (Fig. 71-12). (See Chapter 51 for more information).

## **Insulinoma Polyneuropathy**

Insulin-secreting tumors have been associated with a paraneoplastic polyneuropathy in dogs. Affected dogs may initially have a stiff rear limb gait, but this progresses to generalized weakness, muscle atrophy, and hyporeflexia. Treatment of the insulinoma may result in resolution of the polyneuropathy. (See Chapter 52 for more information.)

# **Paraneoplastic Polyneuropathy**

Although clinically significant paraneoplastic neuropathies are infrequently recognized in dogs and cats, histologic



#### FIG 71-10

**A**, Acute, severe lower motor neuron paralysis of the rear limbs occurred in this 6-week-old Dalmatian puppy. The limbs were cool, and no femoral pulses were palpable. **B**, The footpads on the front feet were warm and pink, whereas those on the rear feet were cool and pale. Ultrasound examination revealed a caudal aortic thrombus. **C**, Acute lower motor neuron paralysis in the left hindlimb of a 9-year-old cat caused by an iliac artery thrombus. **D**, The left hindlimb was cool, had no palpable femoral arterial pulse, and had pale footpads.

lesions of polyneuropathy are evident in most dogs with cancer. LMN paresis caused by paraneoplastic polyneuropathy has been reported in dogs with bronchogenic carcinoma, hemangiosarcoma, mammary carcinoma, pancreatic carcinoma, prostatic carcinoma, lymphoma, and multiple myeloma. Complete systemic evaluation and cancer search (thorough physical examination, thoracic and abdominal radiographs, abdominal ultrasound, lymph node aspirates)

are warranted in all animals presented for chronic progressive LMN dysfunction. In some cases treatment or removal of the offending neoplasm is associated with resolution of the clinical signs of polyneuropathy.

# **Immune-Mediated Polyneuritis**

Polyneuritis can occur as a primary immune-mediated disorder or as a component of a systemic immune-mediated

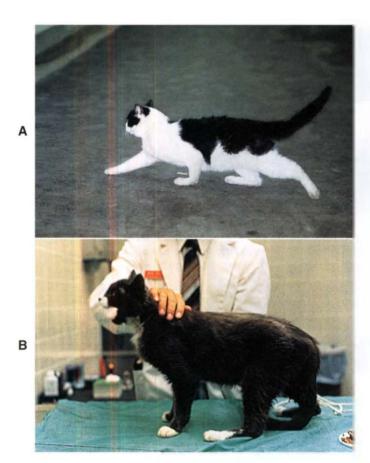


FIG 71-11
Plantigrade stance in A, an 11-year-old cat, and B, a 6-year-old cat with polyneuropathy caused by diabetes mellitus.

disease such as systemic lupus erythematosus (SLE; Fig. 71-13). Weakness and exercise intolerance may be the initial manifestations, followed by progressive muscle atrophy and hyporeflexia. Some animals have concurrent cranial nerve dysfunction. Tests should be performed to eliminate endocrine and neoplastic causes of neuropathy and to investigate other systemic manifestations of immune-mediated disease. Screening tests should include evaluation of a CBC, measurement of protein in the urine (i.e., protein : creatinine ratio), and analysis of synovial fluid. Skin lesions, if present, should be biopsied, and blood should be submitted for an antinuclear antibody (ANA) titer. Immunosuppressive therapy should be initiated using prednisone and azathioprine. The short-term prognosis for recovery may be good, but there is a tendency for these disorders to relapse and progress over time.

## **Idiopathic Polyneuropathy**

Demyelinating polyneuropathies with no known etiology have been observed in dogs and cats. Systemic evaluation does not reveal an underlying cause. Often, they are treated as an immune-mediated disorder, with no response.



FIG 71-12
Plantigrade stance and weak gait in a 6-year-old Newfoundland with severe hypothyroid neuropathy. All neurologic signs and weakness resolved, and the dog lost 60 pounds within 12 months of thyroid hormone supplementation.



BOX 71-1

Generalized Disorders of the Peripheral Nerves and the Neuromuscular Junction

#### **Chronic Lower Motor Neuron Paresis**

Breed-associated degenerative neuropathies Metabolic disorders

Melabolic alsolaers

Diabetes mellitus

Hypothyroidism

Paraneoplastic disorders

Insulinoma

Other tumors

Immune-mediated polyneuritis

Primary immune

Systemic lupus erythematosus

Idiopathic polyneuropathy

Delayed organophosphate intoxication

Ehrlichiosis (?)

#### Acute Lower Motor Neuron Paresis/Paralysis

Acute canine polyradiculoneuritis (Coonhound paralysis)
Neospora polyradiculoneuritis

Tick paralysis\*

Botulism\*

# Episodic Weakness, Normal Neurologic Exam

Myasthenia gravis\*

<sup>\*</sup>Disorder of the neuromuscular junction.



FIG 71-13 A 4-year-old Great Dane with severe weakness, hyporeflexia, and muscle atrophy caused by polyneuritis resulting from systemic lupus erythematosus. The dog also had dermatitis, polyarthritis, glomerulonephritis, and a positive antinuclear antibody test. Polyneuritis was confirmed on postmortem examination.

#### **Ehrlichiosis**

Rarely, dogs are identified with a mononeuropathy or polyneuropathy and concurrent positive serologic or polymerase chain reaction (PCR) testing for Ehrlichia canis, but they have no other clinical signs indicating ehrlichiosis. In some dogs the neuropathy resolves after appropriate treatment with doxycycline (5 mg/kg, administered orally q12h) or imidocarb dipropionate (5 mg/kg, administered twice intramuscularly, 14 days apart). Definitive evidence for a causative relationship is lacking.

# **Delayed Organophosphate Intoxication**

Some toxins, including organophosphates, heavy metals, and industrial chemicals, can cause peripheral nerve damage. Organophosphates, in particular, can have a delayed neurotoxic effect that may be related to their inhibition of neurotoxic esterase, an enzyme necessary for nutrient transport within neurons. Exposure to the toxin may have been a single severe exposure with clinical signs of acute intoxication or chronic mild to moderate exposure repeated over weeks or months without acute signs. Between 1 and 6 weeks after exposure a neuropathy develops. Affected animals are weak but do not have classic autonomic signs of organophosphate intoxication, such as salivation, vomiting, diarrhea, or miosis. With chronic exposure, hair, blood, fat, or liver samples may contain the toxin. Plasma acetylcholinesterase activity is usually low. Toxic neuropathy may be suspected on the basis of nerve biopsy results. Spontaneous improvement should occur in 3 to 12 weeks, provided that the toxic substance is removed and reexposure is prevented.

# **ACQUIRED ACUTE POLYNEUROPATHIES Acute Polyradiculoneuritis**

Acute canine polyradiculoneuritis (ACP) is the only acute polyneuropathy commonly diagnosed in dogs. The disease

affects dogs of any breed and gender, and most affected dogs are adults. A similar disease occurs rarely in cats.

The popular name Coonhound paralysis originates in the fact that in many of the early cases the syndrome developed 7 to 10 days after hunting dogs were bitten by a raccoon. Although raccoon saliva injection does not reliably produce the disorder, it has been shown that in a few susceptible dogs the disorder results from an immune response against some component of raccoon saliva (Fig. 71-14).

Acute polyradiculoneuritis also occurs in many dogs with no possible exposure to raccoons. Previous systemic illness or vaccination (particularly rabies vaccination) has been implicated as an initiating factor in some of these cases, but in most cases no initiating factor can be identified. The pathologic manifestations include extensive demyelination, inflammatory cell infiltration, and disruption of the ventral root components of peripheral nerves. The disease is very similar to allergic neuritis and Guillain-Barre syndrome in humans, making an immunologic pathogenesis suspect.

#### **Clinical Features**

The first clinical sign may be a change in character of the bark; affected dogs sound hoarse. They also develop a stilted, short-strided gait with severe weakness in the rear limbs that ascends rapidly to involve all limbs. Some dogs retain voluntary movement, but most progress to complete paralysis within 5 to 10 days of onset. Neurologic examination reveals remarkably decreased muscle tone, severely diminished or absent reflexes, and rapid muscle atrophy. Some dogs seem to be hyperesthetic, reacting vigorously to mild stimulation such as palpation of the muscles or pinching of the toes. This hyperesthesia is a feature of polyradiculoneuritis that does not occur in association with tick paralysis or botulism, the two major differential diagnoses. Despite the severe paresis or paralysis, dogs remain bright and alert, continue to eat and drink when supported, and can wag their tail vigorously. Bladder and rectum functions remain normal. As a rule, cranial nerves are not involved; no problems with chewing or swallowing exist; neither do any pupillary abnormalities. A small percentage of very severely affected dogs have concurrent bilateral facial nerve paralysis. In a few dogs respiratory paralysis can lead to death.

#### **Diagnosis**

The diagnosis is suspected on the basis of clinical and neurologic findings. The most important and challenging aspect of diagnosis is differentiating this disorder from NMJ disorders causing acute LMN tetraparesis (tick paralysis, botulism, and acute fulminating myasthenia gravis) using clinical features and (when available) electrodiagnostic testing (Table 71-2). Owners should be questioned regarding any possible inciting event or exposure 7 to 14 days earlier. Normal cranial nerve and esophageal function and the presence of hyperesthesia make ACP most likely. Cerebrospinal fluid (CSF) is usually normal, although a mild increase in protein concentration may occur. Electromyography reveals diffuse dener-

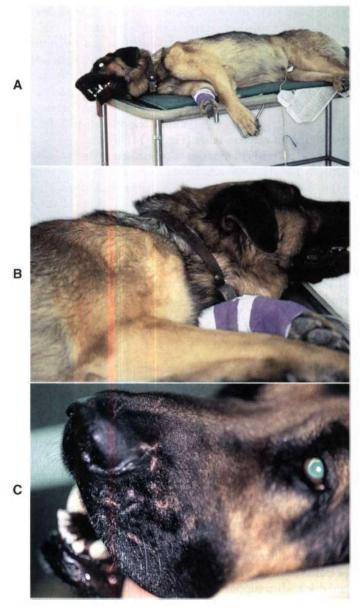


FIG 71-14

A 4-year-old German Shepherd Dog with (A) rapidly progressive ascending lower motor neuron paralysis, (B) severe appendicular muscle atrophy, and (C) healing facial wounds presumed to be from an encounter with a raccoon. The tentative diagnosis in this dog was acute polyradiculoneuritis. Supportive care was initiated, and the dog returned to normal after a prolonged recovery lasting 3 months.

vation (spontaneous activity) after 6 or more days of paralysis, a finding not expected with the NMJ disorders. Definitive diagnosis can also be established by nerve biopsy, but this is rarely necessary.

#### **Treatment**

No specific treatment exists for this disorder. During the initial progressive phase dogs must be monitored for respiratory compromise. Signs typically stabilize after 5 to 10 days, after which the patients can usually be managed with supportive care at home. They may require assistance in sitting up to eat and drink. If possible, they should be kept on an air mattress, waterbed, lounge chair, or bed of straw and turned periodically to prevent lung atelectasis and pressure sores. Corticosteroid treatment is not beneficial.

#### **Prognosis**

The prognosis for recovery is good. Most dogs begin to improve after the first week and are fully recovered within 2 to 4 weeks. Recovery may take 4 to 6 months in severely affected dogs. Some dogs never recover completely, and the prognosis for complete recovery in the cat is poor. Affected animals that have recovered may be prone to recurrences, particularly if exposed again to the initiating antigen.

# **Neospora Polyradiculoneuritis**

**Adult dogs.** Neosporosis can cause a wide range of signs in adult dogs, depending on the site of infection within the nervous system. Paraparesis, tetraparesis, cerebellar signs, muscle pain, seizures, and cranial nerve abnormalities are all reported. Rarely, a rapidly progressive LMN paralysis similar to acute idiopathic polyradiculoneuritis has been reported. Definitive diagnosis is based on a positive serum test for anti-Neospora caninum antibodies, and occasionally the organism can be demonstrated within muscle or nerve biopsies by immunohistochemistry (see Table 69-1). Treatment with clindamycin hydrochloride (10 mg/kg PO q8h for at least 4 weeks) is most effective.

**Puppies.** Young puppies infected transplacentally by *N*. caninum begin showing signs of LMN paraparesis between 6 weeks and 6 months of age. Inflammation of ventral nerve roots and peripheral nerves in the rear limbs results in progressive rear limb weakness, muscle atrophy, and hyporeflexia. Over a period of weeks these LMN signs progress to severe pelvic limb extension as muscle atrophy and fibrosis lock the pelvic limbs in extensor rigidity (see Chapter 69, p. 1062; see also Figs. 69-4 and 69-5). Diagnosis should be suspected on the basis of typical history, clinical, and neurologic findings in a young puppy. Litter mates are often affected. There may be mild to moderate elevations in serum creatine kinase (CK) and aspartate aminotransferase (AST) if muscles are involved. Diagnosis and treatment are as described for adult dogs, with most affected puppies having positive serology and organisms identified in muscle biopsies. Multifocal signs, rapid progression of signs, pelvic limb rigid hyperextension, and delayed treatment are all associated with a poor prognosis for recovery.

# DISORDERS OF THE **NEUROMUSCULAR JUNCTION**

#### TICK PARALYSIS

A flaccid, rapidly ascending motor paralysis has been recognized in dogs infested with certain species of ticks. Most of the reported cases in North America are associated with



TABLE 71-2

Clinical and Diagnostic Differences Between Disorders Causing Rapidly Progressive Lower Motor Neuron Tetraparesis in the Dog

DISEASE	WEAKNESS	MUSCLE TONE	SPINAL REFLEXES	MUSCLE ATROPHY	CRANIAL NERVES	SENSATION	CSF	EMG
Acute Canine Polyradiculoneuritis (Coonhound paralysis)	Generalized weakness, often progressing to paralysis within 5 to 10 days	Decreased	Decreased or absent	Rapid and severe	Hoarse bark Able to eat and drink normally Rarely facial paresis	Hyperesthetic	Normal or increased protein	Denervation after 4-5 days
<ul><li>Tick Paralysis</li><li>Geographic potential for exposure</li><li>Rapid recovery following tick removal</li></ul>	Generalized weakness, rapid progression	Decreased	Decreased or absent	None	Hoarse bark Dysphagia Facial paresis Decreased jaw tone	Normal	Normal	Normal
Botulism — Often a group outbreak	Generalized weakness, often progressing to paralysis within 24 hours	Decreased	Decreased or absent	None	Hoarse bark Dysphagia, mega-esophagus Facial paresis Decreased jaw tone Dilated pupils, absent PLR	Normal	Normal	Normal
Acute Fulminating Myasthenia Gravis  — Some (50%) respond to Tensilon administration (see Box 71-2)	Generalized weakness but maintains ability to move	Decreased	Normal	None	Hoarse bark  Dysphagia, mega-esophagus, aspiration pneumonia  Facial nerve paresis (+/-), fatiguable palpebral reflex	Normal	Normal	Normal

selected strains of *Dermacentor andersoni*, *Dermacentor variabilis*, or *Amblyomma americanum* ticks. The feeding of a female tick results in the elaboration and circulation of a salivary neurotoxin that interferes with acetylcholine release at the neuromuscular junction. Signs occur within 4 to 9 days after tick attachment.

#### **Clinical Features**

Dogs with tick paralysis exhibit a rapid progression from pelvic limb weakness to recumbency, usually resulting in complete LMN paralysis. Muscles are flaccid, and spinal reflexes are decreased or absent. Muscle atrophy does not occur. Pain is perceived normally, with no evidence of hyperesthesia. In most cases the cranial nerves are not significantly affected, but facial weakness, an altered voice, dysphagia, or decreased jaw tone may be recognized. Muscles of respiration may become paralyzed in severely affected patients.

#### Diagnosis

This disease can be confused with other causes of acute tetraparesis such as acute polyradiculoneuritis, botulism, and myasthenia gravis (see Table 71-2). Tick paralysis is diagnosed on the basis of the history, clinical signs, and knowledge of the geographic region. Sometimes a tick can be found on the animal, and diagnosis is confirmed by documenting rapid improvement after tick removal. When electromyography is available, there is no evidence of denervation. Diminished amplitude of the muscle action potential occurs in response to a single supramaximal stimulus, as would be expected with a defect in neuromuscular transmission.

#### **Treatment**

Removal of a tick or dipping the animal in an insecticidal solution results in dramatic recovery within 24 to 72 hours. The prognosis for complete recovery is good when the proper diagnosis is made.

#### **BOTULISM**

Botulism is rarely recognized in dogs and has not been clinically seen in cats. It results from the ingestion of spoiled food or carrion containing a preformed type C neurotoxin produced by the bacterium *Clostridium botulinum*. Only very small amounts of toxin are needed to cause clinical signs. This toxin blocks the release of acetylcholine from the neuromuscular junction, resulting in complete LMN paralysis. Clinical signs occur hours to days after ingestion of the toxin.

#### **Clinical Features**

Affected dogs are weak and develop a short-strided, shuffling gait that rapidly progresses to recumbency. Muscle tone is poor and spinal reflexes are absent, but the tail wag is preserved. Proprioception and pain perception are normal, without hyperesthesia. Affected dogs often have cranial nerve dysfunction resulting in dilated pupils, loss of the pupillary light reflex, weak voice/bark, facial weakness, decreased jaw tone, and dysphagia. Regurgitation resulting from megaesophagus is common. The amount of ingested toxin deter-

mines severity of signs. Clinical signs can last for weeks, and death can occur if respiratory muscles are impaired.

# **Diagnosis**

The diagnosis is based on clinical findings and/or a history of ingestion of spoiled food. Botulism is especially likely if an outbreak of LMN paralysis is seen in a group of dogs. Rabies must be considered as a differential diagnosis in severely affected dogs, but it is usually associated with abnormal mentation. Weakness of the muscles of the face, jaw, and pharynx is much more pronounced with botulism than would be expected with acute polyradiculoneuritis or tick paralysis. When electromyography is available, it reveals the absence of spontaneous activity (no denervation potentials) and diminished amplitude of the muscle action potential in response to a supramaximal stimulus, similar to tick paralysis. Botulinum toxin (type C) may be demonstrated in the blood, vomitus, feces, or stomach contents of affected dogs.

#### **Treatment**

No specific treatment for botulism exists. The administration of laxatives and enemas may help remove unabsorbed toxin from the gastrointestinal tract if ingestion was recent. Administration of commercially available human trivalent antitoxin (types A, B, and E) will not be effective. If Type C antitoxin is available, administration of 10,000 units intramuscularly twice, 4 hours apart, is recommended, but this will simply bind and inactivate circulating toxin that has not yet penetrated nerve endings. Most dogs recover in 1 to 3 weeks with supportive care, although aspiration pneumonia is a common complication during recovery.

# **MYASTHENIA GRAVIS**

Myasthenia gravis (MG) is a neuromuscular disorder characterized by weakness that is exacerbated by exercise and alleviated by rest. Two forms have been described: congenital and acquired. The congenital form of MG results from an inherited deficiency of acetylcholine receptors (AChRs) at the postsynaptic membranes in skeletal muscle. Signs of impaired neuromuscular transmission first become evident in puppies or kittens 6 to 9 weeks old. The disorder has been recognized in English Springer Spaniels, Smooth Fox Terriers, and Jack Russell Terriers, with rare reports in other breeds and a few cats. An unusual, poorly classified transient congenital myasthenic syndrome has also been identified in Miniature Dachshunds; the signs in these dogs resolve with maturation.

The acquired form of MG is a common immunemediated disorder in which antibodies are directed against a portion of the nicotinic AChRs of skeletal muscle. Antibodies bind to the receptors, reducing the sensitivity of the postsynaptic membrane to the transmitter acetylcholine.

The acquired form of MG affects dogs of all breeds and both genders. German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Dachshunds are most commonly affected, but this may merely reflect the popularity of these breeds. Breeds that seem to be at increased risk for acquired MG relative to their popularity include the Akita, some terrier breeds, German Shorthaired Pointers, and Chihuahuas. Young adult dogs (mean age, 2 to 3 years) and old dogs (mean age, 9 to 10 years), make up most of the affected population. Cats are rarely affected, but breed predispositions include the Abyssinian and Somali.

#### **Clinical Features**

The characteristic clinical abnormality in most animals with MG is appendicular muscle weakness that worsens with exercise and improves with rest. Mentation, postural reactions, and reflexes are normal, although reflexes may be fatiguable with repeated stimulation. Excessive salivation and regurgitation is common, caused by megaesophagus (seen in 90% of dogs with acquired MG). Megaesophagus is less common in cats with MG and in congenital MG. Dysphagia, hoarse character of the bark or meow, persistently dilated pupils, and facial muscle weakness are sometimes seen.

A focal form of MG occurs in approximately 40% of affected dogs and 14% of affected cats, causing megaesophagus with no detectable appendicular weakness. Affected dogs exhibit weakness of the pharyngeal, laryngeal, and/or facial muscles and may have a fatiguable palpebral reflex. Approximately 25% to 40% of all dogs with adult-onset megaesophagus suffer from acquired focal MG, so this disorder should always be considered as a differential diagnosis early in the course of evaluation of dogs with megaesophagus.

An acute, fulminating form of acquired MG has also been recognized, causing a rapid onset of severe appendicular muscle weakness. Affected animals are often unable to stand and cannot even raise their head. This form of MG is usually associated with severe megaesophagus and aspiration pneumonia. Profound muscle weakness and severe pneumonia commonly lead to respiratory failure and death.

## **Diagnosis**

MG should be considered as a differential diagnosis in any dog with generalized muscular weakness and in all dogs with acquired megaesophagus. Definitive diagnosis is made by demonstrating circulating antibodies against AChRs by immunoprecipitation radioimmunoassay. This test is readily available (Comparative Neuromuscular Laboratory, University of California, San Diego) and is positive in 85% of all dogs and cats with acquired disease and in 98% of those with generalized acquired disease. False-positive results have not been documented. Although the serum anti-AChR antibody titer does not correlate directly with the severity of clinical signs, dogs with focal MG tend to have lower titers and dogs with acute fulminating MG have the highest titers. Rarely, dogs with acquired MG are negative for circulating AChR antibodies, but immune complexes can be demonstrated in muscle biopsies at the NMJ using immunocytochemical methods. These dogs may have very-high-affinity antibody that remains bound to AChRs and does not circulate or antibodies directed against junctional antigens other than AChRs.



# BOX 71-2

Tensilon Test Protocol

- 1. Place an intravenous catheter.
- 2. Premedicate with atropine (0.04 mg/kg IM) to minimize muscarinic side effects.
- 3. Have equipment available for intubation and ventilation.
- 4. Exercise to the point of detectable weakness.
- Administer Tensilon (edrophonium chloride) IV: 0.1-0.2 mg/kg

When results of the serum test for antibodies are not yet available, or in animals with suspected congenital disease, support for the diagnosis of MG can be gained by demonstrating a positive response to administration of the ultrashort-acting anticholinesterase edrophonium chloride (Tensilon; Box 71-2). This drug inhibits enzymatic hydrolysis of ACh at the NMJ, increasing the effective concentration of ACh and the duration of its effect in the synaptic cleft, optimizing the opportunities for successful interactions between ACh and the AChRs. Most animals with MG exhibit obvious improvement in clinical signs (e.g., resolution of weakness) within 30 to 60 seconds after administration of edrophonium chloride, with the effect lasting approximately 5 minutes. Some dogs with other myopathic and neuropathic disorders may also show some minor improvement, but a dramatic unequivocal response is very suggestive of MG. A failure to respond does not rule out MG. The response can be difficult to assess in dogs and cats with focal MG, and approximately 50% of dogs with acute fulminating MG will have no response because there has been marked antibodymediated destruction of AChRs.

Electrodiagnostic testing (showing a decremental response of muscle action potentials to repetitive nerve stimulation) can be performed as an aid to reaching a definitive diagnosis of MG. However, whenever possible, anesthesia should be avoided in animals with megaesophagus because of the risk of aspiration during recovery.

Thoracic radiographs should be assessed for megaesophagus, aspiration pneumonia, or thymoma, and the animal should be evaluated systemically for underlying or associated immune-mediated and neoplastic disorders. If a cranial mediastinal mass is identified, fine-needle aspiration cytology should be used to confirm the suspicion that it is a thymoma—a tumor that has been identified in fewer than 5% of dogs with acquired MG and in more than 25% of cats. Concurrent immune-mediated disorders are common in dogs with MG, including hypothyroidism, immunemediated thrombocytopenia, immune-mediated hemolytic anemia, hypoadrenocorticism, polymyositis, and SLE. MG may also develop as a paraneoplastic disorder in association with a wide variety of tumors, including hepatic carcinoma, anal sac adenocarcinoma, osteosarcoma, cutaneous lymphoma, and primary lung tumors. Acquired drug-induced

MG has also been documented in hyperthyroid cats being treated with methimazole.

#### **Treatment**

Treatment of acquired MG includes supportive care and the administration of anticholinesterase drugs and occasionally immunosuppressive agents. Surgical removal of thymoma should be considered if identified because many animals with MG will have a decrease in AChR antibody titer and dramatic resolution of their signs after thymectomy. Animals with megaesophagus and regurgitation should be maintained in an upright position during feeding and for 10 to 15 minutes after feeding to facilitate the movement of esophageal contents into the stomach, decreasing the chance of aspiration (Fig. 71-15). If severe regurgitation remains a problem, a gastrostomy tube can be placed to assist in the delivery of nutrients, fluids, and medications (see Chapter 30). Whenever aspiration pneumonia is present, a transtracheal wash (see Chapter 20) should be performed for culture and then aggressive treatment for the pneumonia should be initiated using antibiotics, fluids, nebulization, and coupage. Administration of antibiotics that impair neuromuscular transmission (ampicillin, aminoglycosides) should be avoided.

Anticholinesterase drugs are commonly administered in an attempt to improve muscular strength. Pyridostigmine bromide (Mestinon, 1 to 3 mg/kg, administered orally q8h) has been used in dogs. In cats pyridostigmine bromide syrup (0.25 to 1.0 mg/kg, administered orally q12h, diluted 1:1 with water to decrease gastric irritation) has been recommended. For both dogs and cats the dose must be individu-



Upright feeding in animals with megaesophagus facilitates emptying of esophageal contents into the stomach. Animals should be maintained in this position for 10 to 15 minutes after eating.

alized on the basis of clinical response. Ideally, feeding should be timed to coincide with peak drug effect (2 hours). In dogs initially unable to tolerate oral medication because of severe megaesophagus, neostigmine methylsulfate (Prostigmin 0.04 mg/kg , administered intramuscularly q6-8h) can be used.

If an animal appears to be responding to anticholinesterase treatment but then suddenly gets worse, it is important to determine whether the deterioration is due to underdosage of the anticholinesterase drug (myasthenic crisis) or overdosage (cholinergic crisis). Clinically, these are indistinguishable, but the administration of one dose of edrophonium (Tensilon) allows the clinician to distinguish between them. The animal in a myasthenic crisis improves after edrophonium administration, whereas the condition of an animal in a cholinergic crisis becomes transiently worse or does not change. Dosing adjustments can then be made on the basis of the observed response.

Acquired MG is an immune-mediated disease, and administration of corticosteroids and other immunosuppressive drugs may be associated with a more rapid clinical response, a decrease in AChR antibody, and an improved outcome in some dogs. Ideally, immunosuppressive drugs should be administered only to stable patients without aspiration pneumonia. Because corticosteroids at standard immunosuppressive doses commonly cause transient worsening of muscular weakness in dogs with MG, treatment should be initiated with a low-dose (oral prednisone, 0.5 mg/kg/day) and the dosage gradually increased over 2 to 4 weeks. The oral administration of azathioprine (Imuran, 2 mg/kg/day) or mycophenolate mofetil (CellCept, 10 to 20 mg/kg q12h) alone or in combination with prednisone has been associated with a positive clinical response in some dogs.

#### **Prognosis**

Response to medical management of MG can be good if aspiration pneumonia is not severe and the complications of aspiration and anticholinesterase overdosage are avoided. Severe aspiration pneumonia, persistent megaesophagus, acute fulminating MG, and the presence of a thymoma or another underlying neoplasm are all associated with a poor prognosis for recovery. Many affected dogs die of either acute fatal aspiration or euthanasia within 12 months of diagnosis. Anticholinesterase drugs effectively control appendicular muscle weakness in most animals, but their effect on esophageal function is variable. Response to various immunosuppressive protocols is difficult to determine because most dogs with acquired MG will go into a spontaneous permanent clinical and immunologic remission within 18 months after diagnosis (average, 6.4 months), regardless of the treatment used. Remission is unlikely in animals with thymoma or other neoplastic disease. Sequential antibody determinations in an individual animal are correlated with disease progression or remission; thus it is recommended that AChR antibody concentrations be measured and monitored every 4 to 8 weeks in animals being treated for MG.

#### DYSAUTONOMIA

Dysautonomia is a polyneuropathy affecting both sympathetic and parasympathetic nerves of the autonomic nervous system. Historically, it was recognized as a problem of cats in the United Kingdom, but since the late 1980s it has become a common problem affecting dogs in the Midwest United States, particularly in rural Kansas, Missouri, Oklahoma, and Wyoming. The etiology is unknown, although toxic and autoimmune mechanisms have been proposed. Clinical signs reflect failure of autonomic function in multiple organ systems.

#### **Clinical Features**

The disease affects primarily young adult dogs with a median age of 18 months. Cats are occasionally affected. Affected animals have a rapid onset of clinical signs, which progress over days to weeks. Common presenting complaints are vomiting or regurgitation, diarrhea (constipation in cats), straining to urinate, dribbling urine, photophobia, dyspnea, coughing, depression, and anorexia. Physical examination findings include decreased or absent anal tone, dilated pupils that do not respond to light, dry nose and mucous membranes, and prolapse of the nictitating membrane. The bladder may be distended and easy to express.

## Diagnosis

Diagnosis is suspected on the basis of the observed clinical signs. Thoracic and abdominal radiographs may reveal megaesophagus, aspiration pneumonia, generalized ilcus, and a large distended urinary bladder. The bladder is easily expressed, suggesting diminished urethral sphincter tone. Anal tone is usually decreased. Pharmacologic testing can be used to support the diagnosis. When very dilute (0.05% to 0.1%) pilocarpine (Isoptocarpine 1%, Alcon Laboratories, diluted with saline) is applied to the eye of a dog with dysautonomia, pupillary constriction and nictitating membrane retraction will occur within 60 minutes or less, documenting denervation hypersensitivity. Administration of bethanechol (0.04 mg/kg SQ) may also enable an affected dog with a distended bladder and urine dribbling to void normally. The subcutaneous administration of atropine (0.04 mg/kg) does not produce any change in heart rate in affected dogs. These findings suggest the diagnosis of dysautonomia, but definitive diagnosis requires the demonstration of lesions within the autonomic nervous system at postmortem examination. A loss of nerve cell bodies results in decreased neuron density

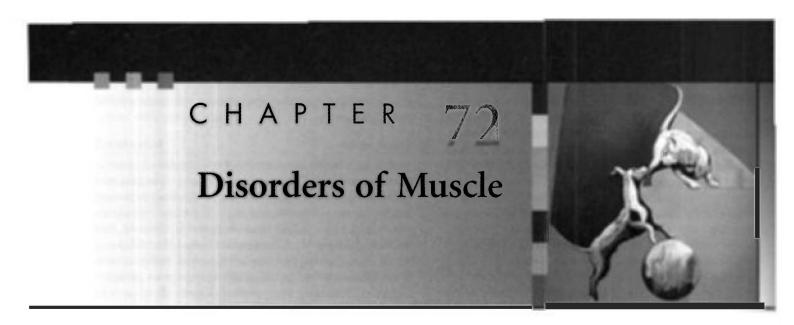
in all autonomic ganglia, especially the pelvic, mesenteric, and ciliary ganglia.

#### **Treatment**

Treatment is largely supportive and includes the administration of fluids, total parenteral nutrition or percutaneous gastrostomy tube feeding, bladder and colon emptying, lubricating eye ointments, and physical therapy. Pilocarpine (1%, one drop q6-12h) may improve lacrimation and decrease photophobia, Subcutaneous bethanechol (0.05 mg/ kg q 8-12h) may improve urinary function, and prokinetic drugs (metoclopramide, cisapride) may improve gastrointestinal tract motility. The prognosis is generally poor, with a mortality rate of about 70% to 90%.

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# CHAPTER OUTLINE

GENERAL CONSIDERATIONS EXERCISE INTOLERANCE INFLAMMATORY MYOPATHIES

Masticatory Myositis Extraocular Myositis Canine Idiopathic Polymyositis

Feline Idiopathic Polymyositis

Dermatomyositis

Protozoal Myositis

ACQUIRED METABOLIC MYOPATHIES

Glucocorticoid Excess

Hypothyroidism

Hypokalemic Polymyopathy

INHERITED MYOPATHIES

Muscular Dystrophy

Centronuclear Myopathy of Labrador Retrievers

Myotonia

Inherited Metabolic Myopathies

INVOLUNTARY ALTERATIONS IN MUSCLE TONE

Opisthotonus and Tetanus

Myoclonus

#### **GENERAL CONSIDERATIONS**

Skeletal muscle functions to maintain posture and produce movement. Patients with generalized muscle disease generally present with weakness. This may manifest as a stiff and stilted gait, trembling while standing, a low head carriage (ventral neck flexion), and exercise intolerance. When a complete nervous system examination is performed, animals with muscle disease have normal postural reactions, are not ataxic, and usually have normal spinal reflexes. Some muscle disorders cause muscle pain and muscle swelling, whereas others cause muscle atrophy and/or fibrosis.

Myopathies in dogs and cats can be either acquired or inherited. Acquired muscle disorders include infectious and immune-mediated inflammatory disorders as well as metabolic and endocrine disorders. Characteristic clinical findings may suggest a specific diagnosis, but muscle biopsy and systemic evaluation are usually required for definitive diagnosis. Metabolic testing may be required to demonstrate and characterize functional abnormalities.

#### **EXERCISE INTOLERANCE**

Reluctance to exercise or inability to exercise for a prolonged period is a common complaint among dog owners. Exercise intolerance can result from orthopedic, cardiovascular, respiratory, hematologic, metabolic/endocrine, neurologic, neuromuscular, and muscular disorders (Box 72-1). When evaluating a dog for exercise intolerance, the veterinarian must perform a careful physical and neurologic examination. Muscle atrophy or pain and weakness at rest with normal postural reactions may suggest a muscle disorder. Joint pain may indicate that the dog has polyarthritis or degenerative joint disease. Abnormalities of cardiac auscultation or arterial pulse character should prompt thorough cardiac evaluation. Routine systemic evaluation with clinicopathologic tests and survey radiographs should be completed. When all examinations and tests are normal at rest, affected dogs should be evaluated while performing the exercise historically associated with their exercise intolerance. Characteristic clinical features during the exercise intolerance (e.g., weakness, stridor, arrhythmia) sometimes provide a clue regarding the etiology. Depending on clinical findings, additional testing may be recommended, including measuring antibodies against acetylcholine receptors (AChRs), continuous electrocardiographic monitoring, thyroid and adrenal function evaluation, arterial blood gas, and measuring preexercise and postexercise parameters (i.e., electrolytes, glucose, creatinine kinase, lactate, and pyruvate). When neurologic examination and ancillary testing suggest a muscular cause for exercise intolerance, muscle biopsies should be performed.

An inherited syndrome of exercise induced collapse (EIC) has been identified in young adult (7 months to 2 years old)



# Important Causes of Acquired Exercise Intolerance in Dogs

#### Orthopedic

Developmental disorders Bone pain Degenerative joint disease Polyarthritis Ligamentous injuries

#### Cardiovascular

Congestive heart failure Cardiac tamponade Cardiac arrhythmias

#### Respiratory

Laryngeal paralysis Airway obstruction Lung parenchymal disease Pulmonary vascular disease Pleural space disease

#### Hematologic

Anemia Polycythemia

#### Metabolic/Endocrine

Hypoglycemia (often intermittent) Hypoadrenocorticism Hypothyroidism Hyperadrenocorticism

#### Neurologic/Neuromuscular

Myasthenia gravis Idiopathic polymyositis Protozoal myositis Inherited myopathies Diskospondylitis Cauda equina syndrome

Exercise induced collapse (EIC) of Labrador Retrievers

Labrador Retrievers being trained for field work. Affected dogs are normal at rest and with moderate exercise. Strenuous exercise in conjunction with excitement results in ataxia and rear limb weakness, sometimes progressing to collapse (Fig. 72-1). During collapse, affected dogs are hyperthermic and they hyperventilate, but physiologic and clinicopathologic parameters are not dramatically different from those of normal exercise-tolerant Labrador Retrievers taking part in the same exercise. Patellar reflexes are absent during collapse, and many affected dogs experience a profound loss of balance (disequilibrium) during collapse and recovery. A few dogs die during an episode of collapse, but most recover within 10 to 20 minutes, with no residual clinical or clinicopathologic abnormalities. Muscle biopsies are normal. The condi-



FIG 72-1

A young Labrador Retriever with the syndrome of exercise induced collapse (EIC) walks with a crouched rear limb gait after 10 minutes of retrieving exercise.

tion is not progressive, so a normal lifespan is expected if participation in the activities triggering collapse is restricted. Diagnosis is made by eliminating other causes of exercise intolerance and demonstrating that the affected dog is homozygous for the causative mutation.

# INFLAMMATORY MYOPATHIES

#### **MASTICATORY MYOSITIS**

Masticatory muscle myositis (MMM) is a common immune-mediated disorder involving only the muscles of mastication in dogs. The masticatory muscles are composed primarily of a unique myofiber (type 2M) that is not present in limb muscles, and in dogs with MMM, IgG is directed against the unique myosin component of these fibers. Masticatory myositis can occur in any breed of dog, but the German Shepherd Dog, the retrieving breeds, the Doberman Pinscher, and other large breeds are most commonly affected. Primarily, young or middle-aged dogs are affected, and no apparent gender predilection exists. The disorder has not been documented in cats.

#### **Clinical Features**

The acute form of the disease involves recurrent painful swelling of the temporal and masseter muscles. Pyrexia, submandibular and prescapular lymphadenopathy, and tonsillitis are variably present. Dogs are reluctant to eat and are usually presented for anorexia and depression. Palpation of the muscles of the head and attempts to open the mouth are met with resistance because of pain.

As this disorder progresses, there is progressive, severe atrophy of the temporal and masseter muscles, resulting in a skull-like appearance of the head. Opening the mouth is no longer painful but is restricted by atrophy and fibrosis of the masticatory muscles (Fig. 72-2). The globes may sink deep into the orbits because of the dramatic loss of muscle mass (see Fig. 66-9). Many dogs will be presented for evaluation at a stage wherein they have pain on opening the





FIG 72-2
Chronic masticatory muscle myositis (MMM) causing
(A) severe temporalis and masseter muscle atrophy and
(B) inability to open the mouth more than a few centimeters in an adult Vizsla.

mouth together with muscle atrophy as they progress from the acute to the chronic form of the disease. Occasionally, dogs will present with nonpainful severe atrophy without any history of signs related to previous acute episodes of pain.

#### Diagnosis

Diagnosis is suspected on the basis of the clinical findings. In dogs with pain on opening the mouth, differentials must include retrobulbar abscess or mass, dental disease, and abnormalities of the temporomandibular joint or the bullae. The severe, nonpainful atrophy observed in chronically affected dogs must be differentiated from atrophy caused by disorders of the trigeminal nerve, widespread polymyositis (any etiology), or systemic disorders such as hypothyroidism or hyperadrenocorticism.

A hemogram may be normal or may reveal mild anemia and neutrophilic leukocytosis; occasionally, a peripheral eosinophilia is found. Serum creatine kinase (CK), aspartate aminotransferase (AST), and globulin concentrations may be increased. Proteinuria sometimes occurs. Circulating antibodies against type 2M fibers can be detected in the serum of many (80%) dogs with acute MMM, but they may not be present in dogs with chronic disease. Electromyography (EMG), when available, can demonstrate the presence of muscle disease in the masticatory muscles and confirm that other muscle groups are unaffected. Histopathologic evaluation of a biopsy from the affected muscles establishes the diagnosis. Fresh and formalin-fixed muscle should be submitted to permit the use of histochemical and immunohistochemical stains to identify antibody bound to type 2M muscle fibers.

#### **Treatment**

The oral administration of corticosteroids (prednisone, 1 to 2 mg/kg q12h) usually results in rapid elimination of pain in acutely affected dogs and an improved ability to open the mouth in chronically affected dogs. After approximately 3 weeks, the dose of corticosteroids can be decreased (to 1 mg/kg q24h) and then gradually tapered over 4 to 6 months to the lowest possible alternate-day dose. Inadequate dosing or treatment for an insufficient period of time is associated with a high rate of relapse. Dogs that do not respond adequately to corticosteroid therapy and dogs that relapse each time the dose is decreased may benefit from the use of other immunosuppressive drugs such as azathioprine (Imuran; Burroughs Wellcome) given 2 mg/kg orally once a day until the patient shows signs of improvement, then every 48 hours. Dogs treated aggressively have a good prognosis for recovery. They should be carefully monitored for relapse (using jaw mobility and discomfort and serum CK), particularly as the corticosteroid dose is tapered. Lifelong treatment may be required.

Historically, it was recommended that dogs with chronic MMM have their jaws opened by force under anesthesia to stretch the fibrous tissue and muscle. This practice is no longer recommended because it does not improve clinical outcome, it increases the inflammation in torn muscle fibers, and it carries an inherent risk of iatrogenic mandibular luxation or fracture.

#### **EXTRAOCULAR MYOSITIS**

A unique form of myositis confined to the extraocular muscles resulting in acute exophthalmos has been described in dogs (Fig. 72-3). Affected dogs are usually young, with a median age at presentation of 8 months. Golden Retrievers and other large-breed dogs are especially susceptible. Bilateral exophthalmos and eyelid retraction are common, often with concurrent chemosis. Vision may be impaired. Serum CK concentrations are usually normal. Orbital sonography confirms swollen extraocular muscles and eliminates retrobulbar abscess or mass as differentials. Definitive diagnosis requires biopsy of affected muscles. Treatment is as for MMM, with a good prognosis for recovery.



**FIG 72-3**Bilateral exophthalmos and upper eyelid retraction caused by extraocular myositis in a Border Collie.

#### **CANINE IDIOPATHIC POLYMYOSITIS**

Idiopathic polymyositis (PM) is a diffuse inflammation of skeletal muscle presumed to be an autoimmune process. Large-breed adult dogs are most commonly affected, with many reported cases in German Shepherd Dogs and Boxers. Newfoundlands may also be overrepresented.

#### **Clinical Features**

Mild to severe weakness and a stiff, stilted gait that may be exacerbated by exercise are the most common features. Muscles are painful in some dogs, whereas nonpainful, severe atrophy occurs in others. Affected dogs may regurgitate as a result of megaesophagus or exhibit dysphagia, excessive salivation, and a weak bark. Signs may be intermittent in mild cases or early in the course of the disease. Some dogs with acute severe disease are pyrexic and experience generalized pain. Neurologic examination reveals normal proprioception, spinal reflexes, mental status, and cranial nerve exam. Muscle atrophy is usually prominent, especially involving the temporalis and masseter muscles.

#### **Diagnosis**

The diagnosis of PM is based on clinical signs, CK determination, EMG, and muscle biopsy. High serum CK (twofold to hundredfold increase) and AST activities are seen in most affected dogs at rest, and even more dramatic increases are common after exercise. Gamma globulins may also be increased. When available, EMG can be performed to document that multiple muscle groups are involved and to select a severely affected muscle for biopsy. A definitive diagnosis of idiopathic PM requires muscle biopsy. Typical histopathologic findings include multifocal necrosis and phagocytosis of type 1 and type 2 myofibers, perivascular lymphocytic and plasmacytic infiltration, and evidence of muscle regeneration and fibrosis. Muscle biopsy results may be normal in some dogs because of the multifocal, patchy nature of the

disease. This should not preclude a diagnosis of myositis if the clinical findings, EMG, and serum CK and AST activities suggest the diagnosis.

PM can occur as an idiopathic primary immunemediated disorder, or it can be secondary to systemic immune-mediated disease (e.g., systemic lupus erythematosus), protozoal infection (e.g., Toxoplasma, Neospora myositis), or systemic neoplasia. All dogs with PM should have a complete blood count (CBC), biochemistry profile, synovial fluid analysis, urinalysis, serum antinuclear antibody (ANA) titer, and protozoal serology and/or immunohistochemical staining of muscle biopsies for protozoal antigens. Assessment of thoracic radiographs and abdominal ultrasound should focus on a search for neoplasia and identification of megaesophagus and aspiration pneumonia. Lymph node, spleen, and liver aspirates and bone marrow biopsy are indicated because lymphoma is the most common cancer associated with PM. If all of these tests are normal, a diagnosis of idiopathic PM is made.

#### **Treatment**

Prednisone administration (1 to 2 mg/kg q12h for 14 days, then q24h for 14 days, then q48h) results in dramatic clinical improvement and recovery for most dogs. In dogs with megaesophagus upright feeding of small meals (see Fig. 71-15) may be beneficial to prevent aspiration. Aspiration pneumonia, if it occurs, should be treated with antibiotics. Prednisone treatment should continue for at least 4 to 6 weeks at decreasing doses, with long-term treatment for 12 months or longer occasionally required. Azathioprine should be administered if the response to prednisone is inadequate.

#### **Prognosis**

The prognosis is good for recovery in dogs without severe megaesophagus or aspiration pneumonia if no underlying neoplastic cause for the PM can be identified.

#### FELINE IDIOPATHIC POLYMYOSITIS

An acquired inflammatory disorder of skeletal muscle similar to canine PM has been described in a few cats. Affected cats experience a sudden onset of weakness with pronounced ventral neck flexion, an inability to jump, and a tendency to sit or lie down after walking short distances. Muscle pain may be evident. Neurologic examination reveals normal mentation, cranial nerves, proprioception, and reflexes.

Diagnosis is made on the basis of clinical features, increases of serum CK and AST activities, and multifocal EMG abnormalities. Many affected cats (70%) are slightly hypokalemic, suggesting a possible relationship between this disorder and hypokalemic polymyopathy. Some clinical features of PM also mimic mild thiamine deficiency; thus evaluation of the response to treatment of affected cats with thiamine (10 to 20 mg/day, administered intramuscularly) and correction of hypokalemia are recommended before proceeding with extensive diagnostic testing for PM.

Serum titers against *Toxoplasma gondii* should be evaluated, as should tests for feline leukemia virus antigen and

feline immunodeficiency virus antibody. A complete drug history should be obtained to eliminate the possibility of drug-induced PM. Thoracic and abdominal radiographs and abdominal ultrasound should be considered to look for an underlying neoplastic cause of the PM. PM has been diagnosed in many cats with thymoma. Muscle biopsy reveals myofiber necrosis and phagocytosis, muscle regeneration, variation in muscle fiber size, lymphocytic inflammation, and fibrosis. Empiric treatment for Toxoplasma myositis is sometimes recommended (clindamycin 12.5 to 25 mg/kg, administered orally q12h); if the animal has a dramatic response to clindamycin, the treatment should be continued for at least 6 weeks. It is important to realize, however, that spontaneous recovery or remission is observed in at least one third of all cats with PM. Corticosteroid therapy (prednisone, 4 to 6 mg/kg/day initially, tapered over 2 months) may aid recovery in some cats. Recurrences are common.

#### **DERMATOMYOSITIS**

Dermatomyositis is an uncommon disease characterized by dermatitis and polymyositis. Familial canine dermatomyositis has been reported in juvenile rough-coated and smoothcoated Collies and in Shetland Sheepdogs (i.e., Shelties). Sporadic cases have been observed in a few other breeds, including Welsh Corgis, Australian Cattle Dogs, and Border Collies. The disease has not been recognized in cats. Skin lesions include erythema, ulcers, crusts, scales, and alopecia on the inner surfaces of the pinnae and on the head and skin surfaces subjected to trauma (e.g., tail, elbows, hocks, sternum; Fig. 72-4). Mild pruritus may occur. Histopathologic findings include hydropic degeneration of basal cells and separation of the dermoepidermal junction. A perivascular mononuclear infiltrate may be seen. Dermatologic lesions appear during the first 3 months of life and may improve or resolve with time. The course often fluctuates.

Dogs severely affected by dermatomyositis may develop signs of concurrent muscle disease, including generalized muscle weakness and atrophy, facial palsy, decreased jaw



A Shetland Sheepdog with typical skin lesions of dermatomyositis. This dog also had megaesophagus and generalized muscular weakness.

tone, and a stiff gait. Mentation, proprioception, and reflexes are normal. Dysphagia is common, as is regurgitation as a result of megaesophagus. EMG reveals spontaneous myofiber discharges, including fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges in affected muscles. Nerve conduction velocities are normal. Muscle biopsies reveal myofiber necrosis with mononuclear cell infiltrates, atrophy, regeneration, and fibrosis. Some dogs with relatively severe dermatologic lesions exhibit no evidence of muscle disease.

Biopsies of skin and muscle, as well as EMG, may confirm a diagnosis of dermatomyositis. Breeding should be discouraged. Dogs with muscular manifestations of this disorder are usually treated with immunosuppressive doses of corticosteroids with a variable response. Dermatologic lesions may respond to oral administration of tetracycline and niacinamide (250 mg of each q8h if <10 kg, 500 mg of each q8h if >10 kg) or pentoxifylline (Trental, 10 to 25 mg/kg q 8-12h).

#### PROTOZOAL MYOSITIS

Myositis caused by T. gondii can occur alone or in conjunction with myelitis, meningitis, or polyradiculoneuritis in dogs and cats, and similar syndromes caused by Neospora caninum can occur in the dog (see Chapters 69 and 71). Clinical signs referable to protozoal myositis typically include muscle pain, swelling or atrophy, and weakness. Increases in CK and AST activities are common, and serum titers for the offending organism may be positive. EMG may reveal spontaneous activity in affected muscles (definitive diagnosis requires muscle biopsy). A mononuclear inflammatory reaction is present, and organisms are often seen. Immunohistochemical stains can be used to identify the organisms and differentiate between T. gondii and N. caninum in affected dogs. Success has been reported in the treatment of protozoal myositis with oral clindamycin (12.5 to 25 mg/kg q12h) for 14 days, but more prolonged treatment (4 to 6 weeks) is advised.

# ACQUIRED METABOLIC MYOPATHIES

In addition to the myopathies associated with infectious and inflammatory disease, myopathies may accompany hyperadrenocorticism (i.e., Cushing's disease), the administration of exogenous corticosteroids, and perhaps hypothyroidism. In cats a myopathy associated with hypokalemia has been recognized.

## **GLUCOCORTICOID EXCESS**

Glucocorticoid excess causes a degenerative myopathy. Spontaneous hyperadrenocorticism or exogenous administration of glucocorticoids, especially in high doses, can result in the syndrome. Muscle weakness and atrophy are common. Rarely, affected dogs develop limb rigidity, stiff gait, and hyperextension of all four limbs.

Diagnosis is suspected on the basis of a history of exogenous steroid administration or clinical findings consistent with steroid excess (e.g., polyuria, polydipsia, hair loss, pendulous abdomen, thin skin). Muscle biopsy reveals nonspecific changes, including type 2 myofiber atrophy, focal necrosis, and fiber size variation. Diagnostic tests for hyperadrenocorticism may confirm the diagnosis (see Chapter 53). Supplementation with L-carnitine, coenzyme Q10 and riboflavin may improve muscular strength. Control of excess glucocorticoids may result in some clinical improvement; however, in most dogs the prognosis is poor for complete resolution of the myopathy.

#### **HYPOTHYROIDISM**

Hypothyroidism may be associated with a mild myopathy in dogs, causing weakness, muscle atrophy, and reduced exercise tolerance. Spinal reflexes are normal unless concurrent polyneuropathy is present. Biopsy reveals mild type 2 myofiber atrophy. Documentation of hypothyroidism and response to thyroid hormone supplementation are required for diagnosis.

#### HYPOKALEMIC POLYMYOPATHY

A polymyopathy linked to decreased dietary intake or increased urinary excretion of potassium leading to total body potassium depletion has been recognized in cats of all breeds, ages, and genders. Cats with chronic renal failure and those consuming acidifying diets are most commonly affected, but cats with polyuria or polydipsia secondary to hyperthyroidism and cats with anorexia from any etiology may also be at risk. Cats with primary hyperaldosteronism because of functional adrenal neoplasia also present with hypokalemic polymyopathy.

The predominant clinical feature in all of these cats is weakness characterized by persistent ventroflexion of the neck (Fig. 72-5); a stiff, stilted gait; and reluctance to move. Some cats exhibit excessive scapular movement during walking. Muscle pain may be apparent, but the neurologic examination is otherwise unremarkable, with normal postural reactions and spinal reflexes. Clinical signs may have an acute onset and be episodic. Serum CK activity is usually high (10 to 30 times normal), serum potassium concentration is decreased (<3.5 mEq/L), and increased fractional urinary excretion of potassium (normal is 4.7-14.3%) may occur. Because most affected cats have renal dysfunction, serum urea and creatinine concentrations may be increased. Interpretation of these parameters and the urine specific gravity can be difficult because hypokalemia can itself decrease renal blood flow and glomerular filtration rate (GFR), interfering with urine-concentrating mechanisms.

EMG abnormalities are found in multiple muscle groups and include frequent positive sharp waves, fibrillation potentials, and occasional bizarre high-frequency discharges with normal nerve conduction velocities. Muscle histopathology usually is normal.

Signs of hypokalemic polymyopathy usually resolve after parenteral or oral supplementation of potassium. Oral treatment with potassium gluconate is recommended for mildly affected cats (Kaon Elixir; Adria Laboratories, Columbus,





FIG 72-5
Feline hypokalemic myopathy resulting in weakness and cervical ventroflexion in (A) a kitten with congenital renal disease and (B) a hyperthyroid cat. The weakness resolved in both cats after potassium supplementation.

Ohio) at a dose of 2.5 to 5.0 mEq/cat twice a day for 2 days, then once a day. The dose administered is adjusted on the basis of serum potassium levels. Cats with more dramatic hypokalemia (less than 2.5 mEq/L) or those with severe muscular weakness causing respiratory compromise require parenteral administration of lactated Ringer's solution, intravenously or subcutaneously supplemented with at least 80 mEq/L of potassium chloride per liter of fluid. Intravenous (IV) supplementation of potassium should not exceed 0.5 mEq/kg/hour. Long-term oral supplementation with potassium gluconate may be required. Periodic monitoring of serum potassium concentration is recommended.

#### INHERITED MYOPATHIES

#### **MUSCULAR DYSTROPHY**

The muscular dystrophies (MDs) are a heterogeneous group of inherited degenerative noninflammatory muscle disorders. Most of the MDs recognized in dogs are associated with an absence of the cytoskeletal protein dystrophin caused by genetic mutation of the dystrophin gene. This very large dystrophin gene is located on the X-chromosome, so MD is

generally inherited as an X-linked recessive trait, clinically apparent in male dogs and transmitted by females that are asymptomatic. Canine X-linked muscular dystrophy (CXMD) has been most completely described in Golden Retrievers but has also been reported in many other breeds of dogs, including the Irish Terrier, Samoyed, Rottweiler, Belgian Shepherd, Miniature Schnauzer, Pembroke Welsh Corgi, Alaskan Malamute, Wire-Haired Fox Terrier, German Shorthaired Pointer, Brittany Spaniel, Labrador Retriever, and Rat Terrier.

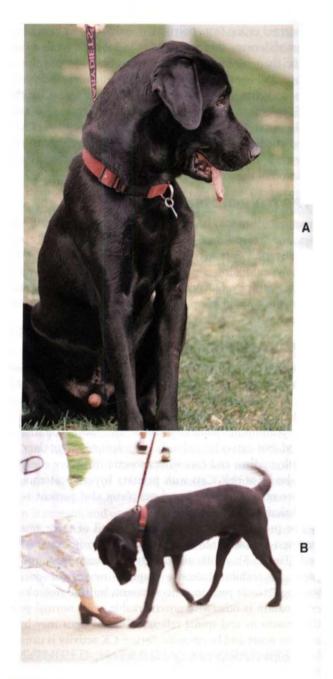
Dogs with CXMD typically show clinical signs at birth or very early in life. Golden Retriever muscular dystrophy (GRMD) has been well described, and despite the fact that all affected male dogs have the same genetic lesion, the severity of clinical expression within a litter is variable. Puppies with GRMD are often stunted even before weaning. Abduction of the elbows, a bunny-hopping gait, and difficulty opening the mouth may be noted. With time, affected puppies develop a progressively stilted gait; exercise intolerance; a plantigrade stance; atrophy of the truncal, limb, and temporalis muscles; and muscle contractures. Muscle strength deteriorates until approximately 6 months of age, when the signs tend to stabilize. Proprioceptive positioning and spinal reflexes are normal, but spinal reflexes may be difficult to elicit once muscle fibrosis and joint contractures occur. Severely affected dogs may develop pharyngeal or esophageal dysfunction. Cardiac failure occurs occasionally.

MD should be suspected when typical clinical signs are seen in a young male puppy of a predisposed breed. Serum CK levels are markedly increased as early as 1 week of age and peak at 6 to 8 weeks of age. Very dramatic increases in CK occur after exercise. EMG reveals pseudomyotonic discharges in most muscles by 10 weeks of age. Biopsies reveal marked myofiber size variation, necrosis, and regeneration with multifocal myofiber mineralization. Immunocytochemical studies document the absence of the sarcolemmal protein dystrophin. No effective treatment exists.

An X-linked MD has also been reported in the cat. Clinical signs first appear at 5 to 6 months of age. Affected cats exhibit marked generalized muscular hypertrophy, protrusion of the tongue, excessive salivation, stiff gait, and bunny hopping. Megaesophagus is common. Serum CK is greatly elevated (often >30,000 U/L). Diagnosis requires muscle biopsy and dystrophin immunostaining.

# CENTRONUCLEAR MYOPATHY OF LABRADOR RETRIEVERS

Centronuclear myopathy (CNM) is a relatively common disorder in the Labrador Retriever. This disorder has been previously reported as hereditary Labrador Retriever myopathy (HLRM), autosomal recessive muscular dystrophy, and type 2 myofiber deficiency. Affected puppies appear normal at birth. Muscular weakness, an awkward gait, exercise intolerance, and muscle atrophy without myalgia typically become apparent by 3 to 5 months of age, with a few puppies showing signs at 6 to 8 weeks. The age of onset and severity of clinical signs varies dramatically among affected litter mates.



A 1-year-old Labrador Retriever with centronuclear myopathy (CNM) exhibiting proximal muscle atrophy; a stiff, stilted gait; and ventroflexion of the neck that worsens with exercise.

Severely affected dogs exhibit a low head carriage and a short-strided, stilted gait (Fig. 72-6). Their back may be arched, and a bunny-hopping gait may develop with exercise. Muscle atrophy may be marked, especially in the proximal limbs and the muscles of mastication. Neurologic examination is normal except for consistent patellar hyporeflexia or areflexia. Megaesophagus causing regurgitation has been seen in a few affected dogs. Clinical signs are worse with stress, exercise, excitement, or cold temperatures. Muscular weakness and atrophy are typically slowly progressive, but a

few affected puppies will be recumbent within 1 to 2 months. Clinical signs stabilize after 12 months of age in mildly affected dogs. Serum CK is normal or moderately elevated, and on EMG examination spontaneous electrical activity and bizarre high-frequency discharges are seen. CNM is histologically characterized by mild to marked variation in fiber size, atrophic type 1 and type II myofibers, replacement of type 2 myofibers by type 1 myofibers resulting in a type 2 predominance, and a marked increase in centralization of nuclei within muscle cells. CNM has an autosomal recessive inheritance pattern. Recently, the causative genetic mutation has been identified and a DNA test is commercially available. No treatment is available, but mildly affected dogs can function as pets.

#### MYOTONIA

Myotonia is a rare disorder of muscle that has been recognized in Chow Chows, Cocker Spaniels, Staffordshire Bull Terriers, Miniature Schnauzers, Labrador Retrievers, Rhodesian Ridgebacks, Samoyeds, West Highland White Terriers, Great Danes, and individual dogs of a number of breeds. Affected kittens have also been identified. Myotonia causes involuntary contraction of muscle that persists after voluntary movement or stimulation. This results from altered chloride conductance, which causes postexcitement depolarization of the muscle membrane and continued contraction. In Miniature Schnauzers the mutant skeletal muscle chloride channel allele has been identified, and a PCR-based test has been developed.

Clinical signs include generalized muscle stiffness and hypertrophy that begin at a young age (i.e., 2 to 6 months). Dogs with myotonia are neurologically normal. No abnormalities of proprioception or mentation exist. Cold weather, excitement, and exercise exacerbate the clinical signs. Affected dogs may remain in rigid recumbency for up to 30 seconds if they are suddenly placed in lateral recumbency. Serum CK and AST activities may be increased, indicating muscle fiber necrosis. Bizarre high-frequency discharges that wax and wane ("dive-bomber sound") are revealed by EMG and, when present, confirm the diagnosis. Muscle biopsy alone is rarely diagnostic. Membrane-stabilizing agents such as procainamide (10 to 30 mg/kg, administered orally q6h) and phenytoin (20 to 35 mg/kg, administered orally q12h) and the sodium channel blocker mexiletine (Mexitil; Boehringer Ingelheim: 8 mg/kg, administered orally q8h), have been beneficial in the treatment of some cases. The avoidance of cold temperatures is also advised. Most dogs are euthanized because of the severity of their signs.

#### INHERITED METABOLIC MYOPATHIES

A number of genetically based metabolic myopathies have been described in dogs and cats. In each of these disorders there is a biochemical defect of the skeletal muscle energy system, resulting in inefficient muscle performance. All of these disorders cause signs of muscle dysfunction, including exercise intolerance; muscular weakness; a stiff, stilted gait; muscle pain; muscle tremors; and muscle atrophy. Mito-

chondrial myopathies, glycogen storage diseases, lipid storage myopathies, and disorders causing nemaline rod accumulation within myofibers have all been reported. Establishing the precise cause of a metabolic myopathy can be difficult because of the wide range of biochemical abnormalities that can arise and the co-dependence of all of the structural proteins making up a muscle fiber. Sometimes metabolic testing can be beneficial; for example, inappropriate lactic acid accumulation with exercise suggests mitochondrial dysfunction. Evaluation of plasma lactate and pyruvate before and after exercise and quantitative analysis of urinary organic acids and plasma, urine, and muscle carnitine will help to document that a metabolic myopathy is present and may help determine the affected biochemical pathway. After metabolic testing, histologic and ultrastructural examination of skeletal muscle should be performed. This metabolic testing and biopsy evaluation should be performed by a laboratory specializing in metabolic disorders of dog and cat muscle. When testing suggests a mitochondrial myopathy or a lipid myopathy, nonspecific treatment with an oral combination of L-carnitine (50 mg/kg q12h), coenzyme Q<sub>10</sub> (100 mg/dog q 24h), and riboflavin (100 mg/dog q 24h) may result in improved muscle strength.

# INVOLUNTARY ALTERATIONS IN MUSCLE TONE

Tetanus, opisthotonus, myoclonus, and dyskinesias are all involuntary alterations of muscle tone that are not the result of muscle disease. Tetanus is a sustained tonic contraction of the muscles. Opisthotonos is a very severe form of tetanus in which spasm of the limb and neck muscles results in lateral recumbency with dorsiflexion of the neck and extensor rigidity of the limbs. Myoclonus is the rhythmic repetitive contraction of a particular group of muscles. Dykinesias, a group of poorly defined movement disorders, are discussed in Chapter 65.

#### **OPISTHOTONOS AND TETANUS**

Loss of consciousness occurring in association with tetanus and opisthotonos (decerebrate rigidity, see Fig. 63-9, A) is seen in dogs and cats with severe brainstem disease caused by infection, trauma, or neoplasia. Brainstem disease in these animals is suspected on the basis of the history, neurologic findings, and results of clinicopathologic tests. Opisthotonos and tetanus with no altered state of consciousness may be seen after trauma to the rostral cerebellum (decerebellate rigidity, Fig. 63-9, B), and in Clostridium tetani infection.

C. tetani is a gram-positive, anaerobic bacillus that produces spores that persist for long periods in the environment. If a deep wound or an area of tissue damage becomes contaminated with these spores, the spores may be anaerobically converted to a vegetative form and a toxin (tetanospasmin) is produced. The toxin ascends peripheral nerves to the spinal cord, where it blocks the release of neurotransmitter

from the inhibitory interneurons (Renshaw cells), releasing extensor muscles from inhibition and resulting in tetany. Cats are more resistant to the toxin than dogs.

Clinical signs of tetanus appear 3 to 20 days after wound infection. Animals with mild or early tetanus show a stiff gait, erect ears, an elevated tail, and contraction of the facial muscles (risus sardonicus; Fig. 72-7). The signs may be most severe in the area of the body adjacent to where the toxin is being produced. In severe disease the animal is recumbent and shows extensor rigidity of all four limbs and opisthotonos. The animal may die as a result of an inability to ventilate adequately. Tetanus is diagnosed on the basis of clinical signs and the history of a recent wound.

Treatment should consist of rest, immediate wound debridement, antibiotics, neutralization of the toxin, and intensive supportive care. Initially, aqueous penicillin G is



FIG 72-7
Tetanus in two dogs, with the erect ears and risus sardonicus resulting from contraction of the head and facial muscles. Both dogs had wounds on a forelimb, which were

presumed to be the site of entry of the toxin.

administered intravenously (40,000 U/kg q8h), after which the procaine salt can be given by intramuscular injection (40,000 U/kg q12h). Alternatively, metronidazole (10 to 15 mg/kg IV q8h) may be administered; it is bactericidal against most anaerobes and achieves a therapeutic concentration even in necrotic tissues. Antibiotics are administered for 2 weeks or until clinical recovery occurs.

A test dose of tetanus antitoxin (equine origin) is injected intradermally 15 to 30 minutes before the administration of a treatment dose. If no wheal develops, the antitoxin is administered intravenously (200 to 1000 U/kg; maximum, 20,000 U). This dose is not repeated because a therapeutic blood concentration persists for 7 to 10 days after a single injection, and repeated administration of antitoxin increases the chance of an anaphylactic reaction. The injection of a small dose of antitoxin (1000 U) just proximal to the wound site may be beneficial in dogs and cats with localized tetanus.

The animal is maintained in a quiet, dark environment. Muscle spasms are controlled with oral or IV diazepam (0.5 to 1 mg/kg, as needed) and IV chlorpromazine (0.5 mg/kg q8h) or intramuscular acepromazine (0.1 to 0.2 mg/kg q6h). Phenobarbital (2 mg/kg q8h, administered intravenously or intramuscularly) or pentobarbital (5 to 15 mg/kg IV to effect) may be administered as needed. IV fluids are administered, and nutritional support is achieved using nasogastric or gastrotomy tube feeding. The animal is hand-fed as soon as it is able to prehend food and swallow. In some animals urinary and fecal retention must be managed by repeated catheterization and enemas. Improvement is usually noticeable within 1 week, but signs may persist for 3 to 4 weeks. The prognosis is poor if the signs progress rapidly, but approximately 50% of affected dogs survive if managed intensively.

#### **MYOCLONUS**

Myoclonus is a rhythmic, repetitive contraction of a portion of a muscle, an individual muscle, or a group of muscles occurring as often as 60 times per minute. These rhythmic contractions do not abate during sleep or general anesthesia. Limb and facial muscles are most often involved. Myoclonus is most commonly associated with canine distemper meningoencephalomyelitis, but other focal inflammatory or neoplastic lesions of the spinal cord can also produce myoclonus in rare cases. The prognosis for resolution of the myoclonus is grave.

Familial reflex myoclonus has been recognized in 4- to 6-week-old Labrador Retriever puppies. Clinical signs include intermittent spasms of the axial and appendicular muscles with occasional episodes of opisthotonos. These signs worsen when the animal is stressed or excited. Treatment with diazepam and clonazepam has not been successful. The prognosis for recovery is grave.

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# Drugs Used in Neurologic Disorders

DRUG NAME (TRADE		RECOMMENDED DOSE		
NAME)	PURPOSE	DOG	CAT	
Acepromazine	Relaxation (tetanus)	0.1-0.2 mg/kg IM q6h	same	
Acetylcysteine	Antioxidant for degenerative myelopathy	25 mg/kg PO q8h daily × 14d then q8h on alternate days	30.110	
Activated charcoal (1 g/5 ml water)	Gastrointestinal adsorbent	10 ml/kg	same	
Aminocaproic acid	Antiinflammatory for degenerative myelopathy	500 mg PO q8h	not used	
Ampicillin	Antibiotic	22 mg/kg PO q8h or 22 mg/kg IV, SC, IM q6h	same	
Amoxicillin with clavulanic acid (Clavamox)	Antibiotic	12.5-25 mg/kg PO q8h	same	
Apomorphine	Emetic	0.08 mg/kg SC or 6 mg (1 crushed tablet) in conjunctival sac	use alternative (xylazine)	
Atropine	Antidote for cholinergic toxins	0.5 mg/kg IV then 1.5 mg/kg SC q6-8h	same	
Azathgioprine (Imuran)	Immune-mediated diseases	2.0 mg/kg PO q24h	do not use	
Bethanechol (Urecholine)	Treat bladder atony	0.04 mg/kg PO, SC q8h	same	
Calcium gluconate (10%)	Treat hypocalcemia	0.5-1.0 ml/kg IV	same	
Cefotaxime	Antibiotic	20-40 mg/kg IV qóh	same	
Ceftriaxone	Antibiotic	25 mg/kg IV or SC q24h	same	
Cephalexin (Keflex)	Antibiotic	20-40 mg/kg PO q8h	same	
Chlorpromazine (Thorazine)	Antiemetic (vestibular)	1-2 mg/kg IV q8h	same	
Clindamycin	Antibiotic	10-15 mg/kg PO q8h	same	
Clorazepate	Anticonvulsant	1-2 mg/kg PO q12h	same	
Cyclosporine (Neoral)	Treat GME	6 mg/kg q12h	none	
Cytosine arabinoside (Cytosar)	Treat GME	50 mg/m <sup>2</sup> SC q12h on 2 consecutive days q21d	none	
Dextrose (50%)	Treat hypoglycemia	2 ml/kg	same	
Diazepam (Valium)	Anticonvulsant, chronic seizure management	0.3-0.8 mg/kg PO q8h	same	
	Status epilepticus	5-20 mg IV or rectal	5 mg IV or rectal	
Diphenhydramine	Antiemetic (vestibular)	2-4 mg/kg IM or SC	1-2 mg/kg IM or SC	
Doxycycline	Antibiotic	5-10 mg/kg PO, IV q12h	same	
Edrophonium chloride (Tensilon)	Tensilon test for myasthenia gravis	0.1-0.2 mg/kg IV	0.2-1.0 mg/IV	



DRUG NAME (TRADE		RECOMMENDED DOSE		
NAME)	PURPOSE	DOG	CAT	
Enrofloxacin (Baytril)	Antibiotic	5 mg/kg PO, SC, IV q12h	5 mg/kg PO or IM q12h	
Felbamate (Felbatol)	Anticonvulsant	15 mg/kg q8h	same	
Furosemide (Lasix)	Diuretic	2-4 mg/kg IV, IM	same	
rorosemide (Lasix)	To decrease intracranial pressure	1 mg/kg IV	same	
Gabapentin (Neurontin)	Anticonvulsant	10-20 mg/kg q8h	same	
lpecac Syrup	Emetic	6.6 ml/kg PO	same	
Leflunomide	Treat GME	4 mg/kg PO q24h initial Maintenance 0.5 mg/kg/day	none	
Levitiracetam (Keppra)	Anticonvulsant	20 mg/kg PO q8h	unknown	
Mannitol 20%	Cerebral edema treatment	1-3 mg/kg IV over 15 min	same	
Meclizine	Vestibulosedative antiemetic	1-2 mg/kg q24h	none	
Methocarbamol (Robaxacin)	Muscle relaxant	20 mg/kg PO q8-12h	none	
Methylprednisolone sodium succinate (SoluMedrol)	Spinal trauma (acute)	20-40 mg/kg IV	same	
Metronidazole (Flagyl)	Antibiotic	10-15 mg/kg PO q8h	same	
0.0077		7.5 mg/kg IV q8h	same	
Mycophenolate mofetil (CellCept)	Treat GME/Myasthenia gravis	20 mg/kg PO q12h × 30d, then 10 mg/kg q12h	none	
Neostigmine methylsulfate (Prostigmin)	Myasthenia gravis	0.04 mg/kg IM q6-8h	same	
Pentobarbital	Anticonvulsant/anesthetic	5-15 mg/kg IV to effect	same	
Phenobarbital	Anticonvulsant	2.5 mg/kg PO q12h adjust based on blood level	same	
Phenoxybenzamine	Decrease urethral smooth muscle tone	0.25-0.5 mg/kg PO q8h	2.5-7.5 mg q12h	
Potassium bromide	Anticonvulsant	15-20 mg/kg PO q12h adjust based on blood level	none	
Potassium gluconate (Kaon Elixir)	Treat hypokalemia	None	2.5-5.0 mEq PO q12h	
Pralidoxime chloride (2-PAM)	Treat organophosphate intoxication	20 mg/kg IM q12h	same	
Prednisone	Immunosuppression	2-4 mg/kg PO q24h	2-6 mg/kg PO q24h	
	Antiinflammatory/antiedema	0.5-1.0 mg/kg PO/24h	same	
Procainamide	Myotonia	10-30 mg/kg PO qóh	none	
Propofol	Anticonvulsant/anesthetic	4 mg/kg IV to effect	same	
Procarbazine (Matulane)	Treat GME	25-50 mg/m² PO q24h × 30d then q48h	none	
Pyrimethamine	Toxoplasmosis	0.25-0.5 mg/kg PO q12h	same	
Pyridostigmine bromide (Mestinon)	Myasthenia gravis	1-3 mg/kg PO q8-12h	0.25-1.0 mg/kg PO q12h	
Thiamine (B12)	Treat thiamine deficiency	2-4 mg/kg IM q24h	same	
Trimethoprim/sulfadiazine (Tribrissen)	Antibiotic	15 mg/kg PO q12h	same	
Xylazine (Rompun)	Emetic (cats)	none	0.44 mg/kg IM	
Zonisamide (Zonegran)	Anticonvulsant	5-10 mg/kg PO q12h	<b>3</b> . <b>3</b> ·	

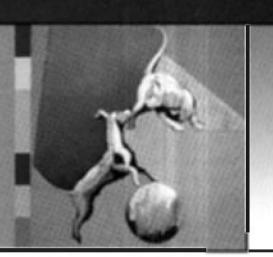
# PART TEN

# Joint Disorders

Susan M. Taylor

# CHAPTER

# Clinical Manifestations of and Diagnostic Tests for Joint Disorders



# CHAPTER OUTLINE

GENERAL CONSIDERATIONS CLINICAL MANIFESTATIONS DIAGNOSTIC APPROACH DIAGNOSTIC TESTS

Minimum Database Radiography Synovial Fluid Collection and Analysis Synovial Fluid Culture Synovial Membrane Biopsy Immunologic and Serologic Tests

#### GENERAL CONSIDERATIONS

Disorders affecting the joints can be divided into two major categories: noninflammatory and inflammatory (Box 73-1). Noninflammatory joint diseases include developmental, degenerative, neoplastic, and traumatic processes. These disorders are discussed in greater detail in surgery textbooks such as those listed in Suggested Readings. Inflammatory joint diseases can be infectious or immune-mediated. When multiple joints are inflamed, polyarthritis is said to be present. Immune-mediated polyarthritis is further classified as erosive or nonerosive disease on the basis of physical examination findings and results of radiographs of affected joints.

Immune-mediated, nonerosive polyarthritis (IMPA) is the most common inflammatory joint disorder recognized in dogs. It results from immune-complex deposition within the synovium, causing a sterile synovitis. IMPA usually occurs as an idiopathic syndrome, but it may also be a feature of systemic lupus erythematosus (SLE) or secondary to antigenic stimulation (reactive polyarthritis) caused by chronic infection, neoplasia, or administration of drugs. In addition, a few breed-associated syndromes of polyarthritis, polyarthritis/meningitis, or polyarthritis/myositis are thought to have a genetic basis in dogs (see Chapter 74).

## **CLINICAL MANIFESTATIONS**

Animals with joint disease are commonly presented with a history of lameness or gait abnormality. Traumatic or developmental disorders typically involve only one joint, with lameness consistently described in the same limb. When multiple joints are affected, a shifting-leg lameness may be reported. Animals with degenerative joint disease typically exhibit low-grade chronic discomfort that causes lameness and a reluctance to exercise without systemic signs of illness. The pain associated with polyarthritis is usually more severe, and affected animals may refuse to walk or may cry in pain when moved or touched (Fig. 73-1). Some animals with polyarthritis are not obviously lame but are presented with a vague history of decreased appetite, fever, weakness, stiffness, or exercise intolerance. Polyarthritis is one of the most common causes of cyclic fevers and nonspecific inflammation in dogs, and because many affected animals do not have obvious joint pain or detectable joint swelling, it is important to maintain a high index of suspicion for this disorder.

# DIAGNOSTIC APPROACH

Animals with nonspecific pain, a stiff gait, reluctance to exercise, or fever of unknown origin should always receive a careful physical examination in an attempt to localize a region of pain or inflammation. Observation of the animal's posture and gait and thorough manipulation and palpation of the spine and the muscles, bones, and joints of each limb are important. Palpation of the bones themselves will elicit pain in animals after trauma and in dogs affected by panosteitis, hypertrophic osteodystrophy, osteomyelitis, or bone



BOX 73-1

Classification of Common Joint Disorders in Dogs and Cats

#### **Noninflammatory Joint Disease**

Developmental

Degenerative

Traumatic

Neoplastic

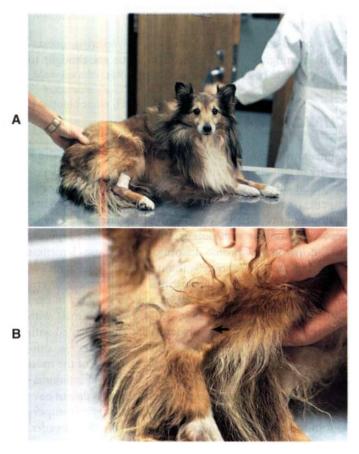
#### **Inflammatory Joint Disease**

Infectious

Noninfectious (immune-mediated)

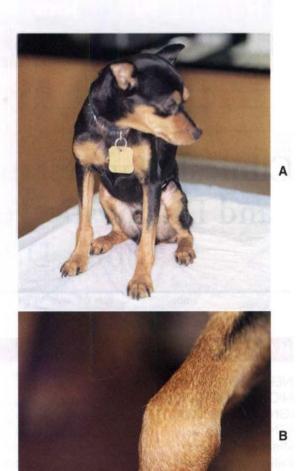
**Nonerosive** 

**Erosive** 



**A,** A 7-year-old Shetland Sheepdog was referred for suspected paralysis. The dog was neurologically normal but refused to rise because of joint pain resulting from idiopathic immune-mediated polyarthritis. **B,** The hock joint is visibly swollen.

neoplasia. Palpation of affected muscles will be painful in animals with myositis or strain/sprain injuries. Pain on palpation or manipulation of the neck could indicate a variety of spinal cord or vertebral abnormalities, intracranial disease, meningitis, or polyarthritis; inflammation of the inter-



**FIG 73-2 A,** A 4-year-old Miniature Pinscher was referred for intermittent fever and depression during the previous year. All joints are palpably and visibly swollen, particularly the carpus **(B)**.

vertebral facetal joints can manifest as neck or back pain (see Box 69-1).

Some animals with joint disease experience obvious discomfort during joint manipulation. Flexing and extending a joint affected by degenerative or erosive disease commonly reveal a restricted range of motion and crepitation, suggesting articular wear, the presence of osteophytes, or other periarticular changes. The stability of the painful joint should be evaluated to assess the integrity of the supporting ligaments. Animals with nonerosive polyarthritis are less likely to have joints that are obviously abnormal on palpation, although joint swelling and pain on manipulation are common (Fig. 73-2). Approximately 30% of dogs with IMPA have no detectable joint swelling or pain, so normal palpation should not deter further diagnostic evaluation for polyarthritis.

Synovial fluid should be collected and evaluated from multiple joints in all dogs and cats with suspected polyarthritis and those with monoarticular disease accompanied by systemic or local signs of inflammation. Synovial fluid analysis is necessary to differentiate inflammatory from noninflammatory joint disease (see Box 73-1). When synovial fluid is inflammatory, the first step is to investigate and eliminate possible infectious diseases as differential diagnoses. Infectious agents causing arthritis include bacteria, Mycoplasma spp., bacterial L-forms, spirochetes, rickettsial agents, and fungi. Diagnostic tests may include a complete blood count (CBC); urinalysis; culture of urine, blood, and synovial fluid; and serology for tick-borne diseases. Thoracic radiographs and fungal serology may also be warranted. Once infectious causes of polyarthritis have been ruled out, immune-mediated conditions should be considered.

Noninfectious IMPA is common in dogs and uncommon in cats. Immune-mediated polyarthritis can occur as an idiopathic syndrome, as a feature of SLE, or secondary to systemic antigenic stimulation (reactive polyarthritis). In reactive polyarthritis the joints are not infected but articular deposition of immune complexes results in synovitis. Reactive polyarthritis has been reported in association with chronic bacterial or fungal infections, neoplasia, or the administration of drugs or vaccines. When the history does not reveal an inciting event, a battery of tests is required to look for systemic evidence of infection or neoplasia (e.g., CBC, thoracic and abdominal radiographs, ophthalmologic examination, bacterial culture of urine and blood, lymph node aspirates, cardiac ultrasonography, abdominal ultrasound) or SLE (e.g., CBC, platelet count, urine protein: creatinine ratio, antinuclear antibody [ANA] titer). Normal results on all of these tests warrant a diagnosis of idiopathic IMPA.

Because most dogs with IMPA have nonerosive disease, radiographs are not always performed during initial evaluation. If dogs with presumed IMPA do not respond quickly and completely to treatment or if joints are unstable or deformed on palpation, radiographs should be taken to evaluate for evidence of erosive disease affecting the articular surfaces, focal "punched out" lesions of lysis in subchondral bone, and proliferation and calcification of periarticular soft tissues. Erosive polyarthritis is an uncommon immunemediated disorder in dogs, with some similarities to human rheumatoid arthritis. This disorder is characterized by progressive joint inflammation, destruction, and deformity. Serologic testing for rheumatoid factor and synovial membrane biopsy aid in the diagnosis of this rare disorder (see p. 1138).

Feline polyarthritis is uncommon. Infectious arthritis has been reported as resulting from bacteria, including bacterial L-forms and Mycoplasma spp., and calicivirus. Periosteal proliferative polyarthritis, an erosive polyarthritis syndrome, has been identified in male cats in association with feline leukemia virus and feline syncytium-forming virus infections. Noninfectious IMPA resulting from SLE also occurs occasionally in cats.

## **DIAGNOSTIC TESTS**

#### MINIMUM DATABASE

Evaluation of a minimum database consisting of a CBC, serum biochemistry profile, and urinalysis should be normal in animals with noninflammatory joint disease. In dogs and cats with polyarthritis it is common to identify a leukocytosis, hyperglobulinemia, and mild hypoalbuminemia. Many of the tick-borne pathogens causing polyarthritis also cause thrombocytopenia. Organisms may be identified within red or white blood cells in animals with some infectious causes of polyarthritis (Fig. 73-3). Proteinuria and hypoalbuminemia will be seen in dogs with concurrent glomerulonephritis. Cats with polyarthritis should always be tested for feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody. Normal clinical pathology does not rule out polyarthritis.

#### RADIOGRAPHY

Radiographs should routinely be taken during initial evaluation whenever only one joint is clinically affected or joint palpation reveals crepitation, instability, or a restricted range of motion. In dogs with presumed IMPA radiographs are recommended if the response to treatment is not as rapid and complete as expected. Radiographic abnormalities of the joints and periarticular region are expected in animals with degenerative joint disease (DJD), chronic septic arthritis, and immune-mediated erosive (rheumatoid-like) arthritis. Results of the physical examination usually help to identify which joints should be radiographically evaluated. Each joint evaluated requires two views (i.e., lateral and anterior/ posterior). Radiographs from patients with infectious polyarthritis caused by rickettsial agents, Lyme disease, or viruses are similar to radiographs from patients with immunemediated nonerosive polyarthritis; typically, the only abnormalities seen are mild joint capsule distention and associated soft-tissue swelling.

Radiographs of the thorax and abdomen and abdominal ultrasound are often recommended in dogs and cats with polyarthritis to evaluate for underlying infectious or neo-

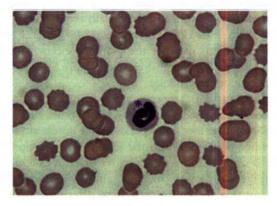


FIG 73-3 Anaplasma phagocytophilium morula in peripheral blood neutrophil from a dog with polyarthritis.

plastic disease. In addition, radiographs of the spine should be performed in dogs with concurrent polyarthritis and neck or back pain to screen for diskospondylitis as a cause for reactive polyarthritis.

Radiography is an important tool, but it is limited. Many of the bony changes seen with DJD and erosive immune disease are not apparent for weeks to months after the onset of signs. Although positive findings contribute a great deal to the diagnosis, negative findings should be interpreted with caution. Sequential radiographic studies may be warranted.

# SYNOVIAL FLUID COLLECTION AND ANALYSIS

Synovial fluid collection and analysis is the most useful test for establishing a diagnosis in dogs and cats with joint disease. It is of greatest value in confirming that a specific joint is abnormal and in differentiating inflammatory from noninflammatory disease. Synovial fluid collection and analysis may also provide information regarding a specific diagnosis.

#### **Collection Method**

Arthrocentesis requires little in the way of expertise or equipment, involves minimal risk to the animal, is inexpensive to perform, and has a high diagnostic yield. In dogs and cats, although synovial fluid can sometimes be collected without sedation or anesthesia, light tranquilization or sedation is usually used to prevent the animal from moving during sample collection and thereby contaminating the sample. Immunologically mediated disease tends to be most prominent in the distal small joints, such as the hock and carpus. Whenever polyarthritis is suspected, synovial fluid should be analyzed from at least six joints, including both carpi, both hocks, and both stifles. Elbows and shoulders should be tapped in animals with poorly localized forelimb lameness. When they are swollen or painful, the smaller metacarpophalangeal and interphalangeal joints can also be sampled. Even if only one joint is clinically affected, synovial fluid should be analyzed from multiple joints.

The hair should be clipped from the area and the skin washed as for surgery. Wearing sterile gloves is necessary if the area where the needle will be inserted is to be palpated. Arthrocentesis in dogs and cats typically requires a 25-gauge needle attached to a 3-ml syringe (Fig. 73-4). A 22-gauge, 1<sup>1</sup>/<sub>2</sub>-inch needle is used for the shoulder, elbow, and stifle joints of larger dogs. Large dogs may require a 3-inch spinal needle to enter the hip joint.

Landmarks for arthrocentesis vary according to personal preference, but some recommended approaches are outlined in Fig. 73-5. After aseptic preparation, the needle attached to the syringe is inserted into the joint. Once the tip of the needle is in the joint, gentle negative pressure is applied to the syringe. Only a very small amount of joint fluid (one to three drops) is needed for the critical determination of viscosity, estimated cell count, differential white blood cell (WBC) count, and culture. The negative pressure on the syringe is released before withdrawal of the needle through



FIG 73-4
Arthrocentesis is performed using a small-gauge needle attached to a 3-ml syringe.

the skin. The appearance of blood should prompt immediate release of suction and withdrawal of the needle. Slides are made immediately (Fig. 73-6), with one drop of synovial fluid used for each slide.

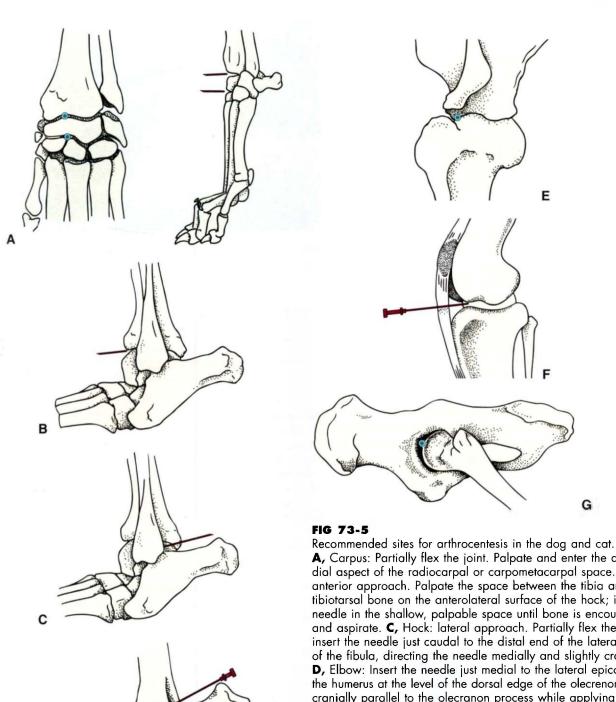
After the collection of samples for cytologic evaluation, a larger sample should be collected for culture and sensitivity. Selection of the most appropriate joint to culture is based on clinical findings or on the gross characteristics of the joint fluid. Aseptic preparation of the joint is repeated, and as much fluid as possible is obtained with gentle suction. This fluid can be either submitted for culture in a sterile tube or directly inoculated into enrichment media.

#### **Analysis of Gross Appearance**

Normal synovial fluid is clear and colorless. Cloudiness or turbidity is seen in any condition that causes red blood cells (RBCs) or WBCs to enter the joint in high numbers. Color change may be an indication of blood contamination or a pathologic condition. Hemorrhage from an earlier puncture attempt or an ongoing disease process typically results in a diffuse red discoloration of the synovial fluid, whereas blood from a traumatic tap is not usually homogeneously mixed with the joint fluid. A yellowish fluid (xanthochromia) may indicate previous hemorrhage into the joint and is occasionally seen in degenerative, traumatic, and inflammatory joint diseases

Normal synovial fluid is very viscous. It forms a long string when allowed to drop from the tip of a needle onto a slide (Fig. 73-7). A thin or watery consistency indicates that





D

A, Carpus: Partially flex the joint. Palpate and enter the anteromedial aspect of the radiocarpal or carpometacarpal space. **B,** Hock: anterior approach. Palpate the space between the tibia and tibiotarsal bone on the anterolateral surface of the hock; insert the needle in the shallow, palpable space until bone is encountered and aspirate. C, Hock: lateral approach. Partially flex the joint, and insert the needle just caudal to the distal end of the lateral malleolus of the fibula, directing the needle medially and slightly cranially. D, Elbow: Insert the needle just medial to the lateral epicondyle of the humerus at the level of the dorsal edge of the olecrenon. Advance cranially parallel to the olecranon process while applying medial pressure on the shaft of the needle. E, Shoulder: lateral approach. With the joint held in partial flexion as if weight bearing, insert the needle just distal to the acromion process cranial to the glenohumeral ligament and direct the needle medially. F, Stifle: With the joint in partial flexion, insert the needle just lateral to the straight patellar ligament equidistant between the distal patella and the tibial tuberosity. Direct the needle slightly medially as it is inserted caudally toward the center of the joint. **G,** Coxofemoral: Support the limb parallel to the table as though the dog were standing. Insert a spinal needle straight in medially just dorsal to the greater

trochanter until bone is encountered, then abduct and medially rotate the limb while advancing the needle ventrally and caudally.

G

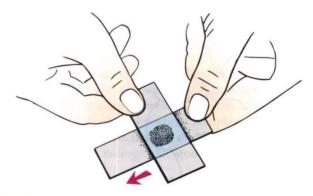


FIG 73-6
Preparing a smear of synovial fluid. A drop of fluid is placed onto a slide. A second slide is used to gently spread the fluid using a pull smear technique.

the synovial fluid is deficient in polymerized hyaluronic acid. This may occur after dilution by serum or through degradation by an intense intraarticular inflammatory reaction.

# **Analysis of Microscopic Appearance**

Cytologic evaluation is the most important aspect of synovial fluid analysis. Usually, only a few drops of synovial fluid are collected, and estimates of cell numbers are made from a stained direct smear of the fluid. One drop of fluid can be placed on a slide and a second slide used to spread the fluid to make a thin smear (see Fig. 73-6). This smear should be air dried and then stained with Diff-Quik or Wrights-Giemsa stain. Because normal synovial fluid contains fewer than 3000 WBCs/µl, no more than three WBCs should be seen per high-dry power (40×) field on a stained smear. Experienced clinicians find simple microscopic scanning of a stained slide of synovial fluid sufficient to estimate cell numbers as normal, mildly increased, or greatly increased.

Normal synovial fluid contains a mixture of large and small mononuclear cells that frequently contain many vacuoles and granules. An occasional neutrophil may be observed, but these cells should represent less than 10% of the total. Blood contamination during synovial fluid collection will result in approximately 1 neutrophil for every 500 RBCs contaminating the fluid. The presence of platelets indicates recent intraarticular hemorrhage or significant blood contamination. Hemosiderin-laden macrophages and erythrophagia confirm prior hemorrhage.

Degenerative joint disease causes a slightly increased cell count (<6000 cells/µl) and an increased volume of synovial fluid, but almost all of the cells are mononuclear cells (Table 73-1). An increase in the number of neutrophils within a joint indicates inflammation of the synovial lining. The more inflamed the synovium, the greater is the concentration of WBCs in the synovial fluid, and the greater the percentage of neutrophils (Fig. 73-8).

In addition to the actual or estimated WBC count and WBC differential, cytologic evaluation of the cells in the joint

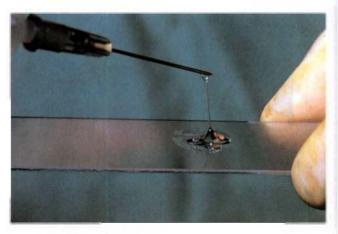


FIG 73-7 Normal synovial fluid is clear and viscous.



TABLE 73-1

Synovial Fluid Cytology in Common Joint Disorders

	WBC/ L	% PMN
Normal	200-3,000	<10
Degenerative	1,000-6,000	0-12
Traumatic	Variable	<25
Septic	40,000-280,000	90-99
Immune-mediated disease		
Nonerosive immune	4,000-370,000	15-95
Erosive arthritis (Rheumatoid-like)	6,000-80,000	20-80

WBC, white blood cell; PMN, polymorphonuclear neutrophil leukocytes.

fluid is important. Neutrophils in the synovial fluid of dogs and cats with immune-mediated disease should have a normal appearance. In acute or severe cases of septic arthritis, it is common to see bacteria within the cells, and neutrophils in the joint may be toxic, ruptured, and degranulated. Organisms may occasionally be observed within the cells in the synovial fluid of animals with polyarthritis caused by rickettsial infections or Leishmania. In dogs with SLE-induced polyarthritis, lupus erythromatosus (LE) cells are in rare cases seen within the synovial fluid (Fig. 73-9).

#### SYNOVIAL FLUID CULTURE

Bacteria are the most common cause of joint infection. Septic arthritis can often be diagnosed on the basis of the appearance of toxic changes within neutrophils and the identification of bacteria on stained smears of synovial fluid. Some organisms, such as *Mycoplasma* spp., do not, however, induce characteristic cytologic abnormalities. Any joint fluid with an increased nucleated cell count and a high percentage of neutrophils warrants a culture. Synovial fluid should be submitted for aerobic and anaerobic culture and for specific *Mycoplasma* spp. culture. Because direct bacterial culture of

synovial fluid is positive in only approximately half of all cases of septic arthritis, failure to grow bacteria in synovial fluid does not rule out septic arthritis. The diagnostic yield can be greatly improved (85% to 100% positive) if infected synovial fluid is collected and inoculated into brothenrichment media (e.g., thioglycolate blood culture bottles), incubated for 24 hours, and then recultured. Microbiologic culture of blood, urine, and synovial membrane biopsy specimens should also be considered to improve chances of recovering the offending organism.

# SYNOVIAL MEMBRANE BIOPSY

Performing synovial membrane biopsy can support a diagnosis already suspected on the basis of the history, physical examination, radiographic studies, and synovial fluid analysis. It may also be used to collect a sample for microbiologic

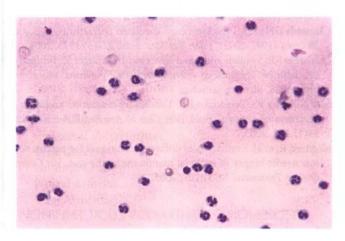


FIG 73-8
Synovial fluid with an increased nucleated cell count consisting primarily of neutrophils from an adult dog with idiopathic immune-mediated polyarthritis.

culture in cases of suspected septic arthritis. Examination of the synovial membrane is especially valuable in the diagnosis of neoplasia and in the differentiation of infectious arthritis from the immune-mediated disorders. An undetermined cause of joint disease or ineffective routine therapy warrants synovial membrane analysis.

Synovial membrane biopsies may be obtained by needle biopsy or surgical arthrotomy. Surgical excision of a wedge of synovial membrane allows visualization of the entire joint and selection of a specific site from which to obtain the biopsy. Needle biopsy of the synovial membrane is quick and minimally traumatic, but samples are small and easily obtained only from the stifle joint. Techniques for both procedures are described in Suggested Readings.

# IMMUNOLOGIC AND SEROLOGIC TESTS Lyme Disease Titers

Infection with the spirochete Borrelia burgdorferi, the etiologic agent for Lyme disease, causes primary infectious synovitis as well as immunologically mediated synovitis resulting from immune complex deposition. Affected dogs develop an antibody response that can be detected using an indirect fluorescent antibody (IFA) test or an enzyme-linked immunosorbent assay (ELISA). Dogs with clinical signs of Lyme disease generally have high titers, but asymptomatic dogs in endemic areas may also have titers greater than 1:8000. Therefore a positive antibody titer merely indicates exposure to the organism and cannot be used to diagnose active disease. The varied, nonspecific clinical signs of Lyme arthritis warrant questioning of the significance of a positive titer. A diagnosis of Lyme disease polyarthritis must rely on a combination of the history (i.e., recent exposure to an area in which the disease is enzootic), clinical signs, elimination of other known causes of polyarthritis, serologic testing, and response to therapy (see p. 1132).

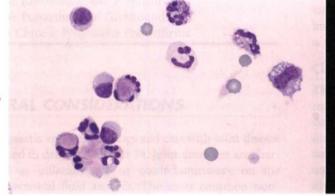




FIG 73-9

Synovial fluid from an adult German Shepherd Dog with polyarthritis. **A,** Some of the cells are lupus erythromatosus cells containing phagocytized, opsonized, amorphous nuclear material. Finding these lupus erythromatosus cells supports a diagnosis of systemic lupus erythromatosus. **B,** This dog also has proteinuria, tongue ulcers caused by vasculitis, and a positive antinuclear antibody test.

#### **Rickettsial Titers**

Serologic testing plays an important role in the diagnosis of Rocky Mountain spotted fever (RMSF), canine monocytc ehrlichiosis, canine granulocytic anaplasmosis, and bartonellosis (see Chapter 96 for more discussion of rickettsial diseases and Chapter 100 for more discussion of bartonellosis). Demonstration of a rising titer is necessary to make the diagnosis of acute RMSF, with a fourfold increase between acute and convalescent titers expected. Demonstration of antibody against *Ehrlichia canis* and *Anaplasma phagocytophilium* indicate prior exposure, with antibody levels remaining elevated for months after successful treatment.

# **Systemic Lupus Erythematosus**

Tests used to help identify SLE include the LE cell test and the ANA test. The LE cell test requires identification of the LE cell, which is a neutrophil or other WBC that has phagocytized opsonized nuclear material. The cytoplasm of these cells is filled with amorphous purple material (see Fig. 73-9). The LE cell test reliability is laboratory dependent, requiring an experienced technician. The ANA test detects circulating antibodies to nuclear material. These antibodies are the most prominent of the autoantibodies associated with canine and feline SLE. The ANA test is a sensitive indicator for the diagnosis of SLE and is positive (>1:10) in 55% to 90% of SLE cases. The ANA is constant from day to day and is less steroid labile than the LE cell test. Unfortunately, a positive ANA test is not specific for SLE, and false-positive results may be seen

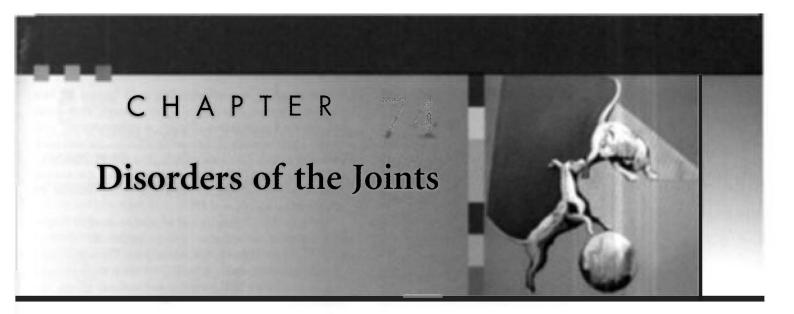
in dogs and cats with many other systemic inflammatory or neoplastic diseases.

#### Rheumatoid Factor

The laboratory test for rheumatoid factor (RF) detects serum agglutinating antibody directed against the patient's own IgG. A titer of 1:16 or higher is generally considered positive, and a titer of 1:8 is considered suspect and should be repeated. The reliability of the test increases with the severity and chronicity of the disease. The test is reported to be positive in 20% to 70% of dogs with erosive (rheumatoid-like) arthritis. Any disease associated with systemic inflammation and immune-complex generation and deposition can result in weak, false-positive results.

# Suggested Readings

- Bennett D: Immune-mediated and infective arthritis. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, Philadelphia, 2005, Elsevier Saunders.
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# CHAPTER OUTLINE

# GENERAL CONSIDERATIONS NONINFLAMMATORY JOINT DISEASE

Degenerative Joint Disease

INFECTIOUS INFLAMMATORY JOINT DISEASES

Septic (Bacterial) Arthritis

Mycoplasma Polyarthritis

Bacterial L Form-Associated Arthritis

Rickettsial Polyarthritis

Lyme Disease

Leishmaniasis

**Fungal Arthritis** 

Viral Arthritis

# NONINFECTIOUS POLYARTHRITIS: NONEROSIVE

Systemic Lupus Erythematosus—Induced Polyarthritis Reactive Polyarthritis

Idiopathic, Immune-Mediated, Nonerosive Polyarthritis

Breed-Specific Polyarthritis Syndromes

Familial Chinese Shar-Pei Fever

Lymphoplasmacytic Synovitis

#### NONINFECTIOUS POLYARTHRITIS: EROSIVE

Canine Rheumatoid-like Polyarthritis Erosive Polyarthritis of Greyhounds

Feline Chronic Progressive Polyarthritis

#### **GENERAL CONSIDERATIONS**

The diagnostic approach to dogs and cats with joint disease is discussed in detail in Chapter 74. Joint disorders are characterized as inflammatory or noninflammatory on the basis of synovial fluid analysis. The most common noninflammatory joint disease is degenerative joint disease (DJD), with characteristic clinical and radiographic featuers. When synovial fluid is inflammatory, careful evaluation for an infectious cause should be performed. Noninfectious inflammatory polyarthritis is considered to be immune mediated. Animals with immune-mediated polyarthritis

usually have primary idiopathic immune-mediated disease, but some have systemic lupus erythematosus (SLE), and others develop immune complex—mediated polyarthritis secondary to prolonged systemic antigenic stimulation (reactive polyarthritis; see Chapter 73). Most immune-mediated polyarthritis syndromes are nonerosive. Disorders causing radiographic evidence of bone destruction (erosive disease) are rare.

# NONINFLAMMATORY JOINT DISEASE

#### **DEGENERATIVE JOINT DISEASE**

#### Etiology

Degenerative joint disease (DJD), or osteoarthritis, is a chronic, progressive disorder of joints that results in articular cartilage damage and degenerative and proliferative changes in the periarticular tissues. Joint instability, trauma, and developmental orthopedic diseases are the most commonly identified underlying causes. Although considered noninflammatory on the basis of synovial fluid cytology, inflammatory mediators are involved in the clinical manifestations and progression of DJD. It is estimated that approximately 20% of the adult canine population in North America is affected by DJD in at least one joint.

#### **Clinical Features**

The clinical signs of DJD are usually insidious in onset and confined to the musculoskeletal system, with no associated systemic signs. Lameness and stiffness may initially be prominent only after periods of overexertion and may worsen in cold and damp weather. Mildly affected dogs may "warm out" of their lameness with exercise. As DJD progresses, fibrosis and pain lead to decreased exercise tolerance; constant lameness; and, in severe cases, muscular atrophy. Either a single joint or multiple joints may be affected.

#### **Diagnosis**

DJD is usually diagnosed on the basis of history, physical examination findings, and characteristic radiographic fea-



FIG 74-1 Close-up mediolateral radiograph of left elbow joint of a 14-month-old female German Shepherd Dog with severe degenerative changes secondary to a fragmented coronoid process.

tures. Clinical examination may reveal pain in the affected joint or joints, decreased range of motion, crepitation on flexion and extension of the joint, and (perhaps) appreciable joint swelling. Radiographic changes characteristic of DJD include joint effusion, subchondral bone sclerosis, joint space narrowing, periarticular osteophyte formation, and bone remodeling (Fig. 74-1). A predisposing condition is often identified, such as trauma, rupture of supporting ligaments, poor conformation, or a congenital deformity. Animals with DJD do not exhibit the fever, leukocytosis, and depression commonly seen in animals with inflammatory joint disease.

Synovial fluid from a joint with DJD may be slightly less viscous than normal. The total nucleated cell count is normal or slightly increased, but it rarely exceeds 5000 cells/ l. Characteristically, mononuclear cells constitute at least 80% of the cells and neutrophils are rare (<10%). Acute joint injury or ligament rupture occasionally incites a more inflammatory response, with moderate increases in synovial fluid neutrophils for days to weeks following injury.

## **Treatment**

The goals of treatment in dogs with DJD are to alleviate discomfort and prevent further degeneration. Surgical intervention may be necessary to stabilize the joint or correct a deformity and to relieve discomfort. Medical treatment is symptomatic and nonspecific. Weight reduction may decrease the stresses acting on the joint. Rest often helps to decrease the discomfort associated with acute exacerbations of disease. High-impact exercise, such as running and jumping, should be discouraged, whereas low-impact exercise done in moderation, such as swimming and leash walking, is recommended to maintain the animal's strength and mobility. Other forms of physical therapy may include

passive range of motion exercises, cold (acute) or heat (chronic) therapy, muscle and joint massage, ultrasound, and electrical stimulation. Dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and antioxidants (vitamin E, vitamin C, beta carotene, zinc and selenium) or feeding commercial "joint diets" containing these supplements may decrease the inflammation and pain of DJD.

Pharmacologic therapies may be used to decrease further degradation of the articular cartilage, inhibit the release of inflammatory mediators, and control pain. The nonsteroidal antiinflammatory drugs (NSAIDs) are often recommended because of their antiinflammatory and analgesic effects. The primary action of most NSAIDs is reversible inhibition of cyclooxygenase, preventing synthesis of the prostaglandins responsible for pain and inflammation. Selective inhibition of two forms of cyclooxygenase (COX-1 and COX-2) may explain some of the differences in efficacy and toxicity among the available NSAID agents. Preferential inhibition of COX-2 with relative sparing of COX-1 by an NSAID may be associated with improved control of inflammation and decreased potential for gastric irritation and ulceration or renal toxicity. Renal function should be assessed before prescribing any NSAID, after 7 days of treatment, and then at least every 6 months during chronic administration. Owners should also be instructed to monitor for inappetence, vomiting, or melena, which could indicate gastrointestinal toxicity. Because the clinical response to each NSAID varies between dogs, it is often advised to switch drugs to determine which one is most effective (Table 74-1). When switching from one NSAID to another, a washout period of at least 3 days without NSAID administration is recommended to prevent toxicity. In dogs that are intolerant of NSAIDs or those that require further analgesia, oral tramadol (2-5 mg/kg q8-12h) can provide relief.

Oral and injectable disease-modifying chondroprotective agents may improve cartilage biosynthetic activity, decrease synovial inflammation, and inhibit intraarticular degradative enzymes. Oral glucosamine and chondroitin sulfate can be administered separately or in combination. An orally administered combination of glucosamine HCl, chondroitin sulfate, and manganese ascorbate has also been recommended (Cosequin RS, 1 to 2 tablets q24h in cats or small dogs; Cosequin DS, 2 to 4 tablets q24h in large dogs; Nutramax Labs). Polysulfated glycosaminoglycans or pentosan polysulfate may be beneficial when administered intramuscularly (see Table 74-1). Hyaluronic acid is a nonsulfated glycosaminoglycan that can be administered as an intraarticular injection to improve synovial viscosity and decrease inflammation. To achieve the maximum theoretic benefit from all of these products, they should be administered before DJD has occurred. Therefore they may be indicated for the treatment of dogs that have sustained trauma or undergone surgery that is known to have damaged articular cartilage. Clinical trials are necessary to evaluate their efficacy.



Dosages of Selected Drugs for the Treatment of Degenerative Joint Disease in Dogs

GENERIC NAME	DRUG NAME	DOSE
Nonsteroidal Antiinflammatory Drugs (N	NSAIDs)	
Acetylsalicylic acid	(Aspirin)	10-20 mg/kg PO q8-12h acid
Carprofen	(Rimadyl)	2.2 mg/kg PO q12h
Deracoxib	(Deramaxx)	1-2 mg/kg PO q24h
Etodolac	(Etogesic)	10-15 mg/kg PO q24h
Firocoxib	(Previcox)	5mg/kg PO q24h
Meloxicam	(Metacam)	0.2 mg/kg PO once, then 0.1 mg/kg PO q24h
Piroxicam	(Feldene)	0.3 mg/kg PO q48h
Disease-Modifying Chondroprotective As	gents	
Chondroitin sulfate		15-20 mg/kg PO q12h
Glucosamine		15-20 mg/kg PO q12h
Pentosan polysulphate	(Pentosan 100)	3 mg/kg IM q7d
Polysulfated glycosaminoglycans	(Adequan)	3-5 mg/kg IM q4d for 8 tx, then q30d
Analgesics	, , ,	
Tramadol		2-5 mg/kg PO q8-12h
Gabapentin	(Neurontin)	5-20 mg/kg PO q8-12h

PO, oral; IM, intramuscular.

# INFECTIOUS INFLAMMATORY JOINT DISEASES

# SEPTIC (BACTERIAL) ARTHRITIS

#### Etiology

Septic arthritis can result from a blood-borne infection or from direct inoculation of a joint. Bacterial infection of multiple joints suggests hematogenous spread of bacteria from a local site of infection. This is uncommon, except in neonates with omphalophlebitis, immunosuppressed animals, and dogs with preexisting polyarticular DJD. Monoarticular septic arthritis is much more common and usually follows direct inoculation of bacteria into a single joint as a result of surgery, a bite wound, foreign body penetration, or trauma. *Staphylococcus* spp., *Streptococcus* spp., and coliform organisms are most often incriminated in the dog, and *Pasteurella* spp. are most commonly identified in cats. Septic arthritis, regardless of the cause, is more common in dogs than cats, is most common in large-breed dogs, and more frequently affects males than females.

#### Clinical Features

Animals with septic polyarthritis are often systemically ill, febrile, and depressed. The affected joints are usually very painful, especially when manipulated, and may be palpably distended with synovial fluid. The periarticular soft tissues may be inflamed and edematous. Septic arthritis stemming from bacteremia usually involves one or a few of the large proximal joints.

# Diagnosis

For septic arthritis to be diagnosed, bacteria must be identified in cytologic preparations of synovial fluid or cultured in synovial fluid, blood, or urine from an animal with appropriate clinical signs and inflammatory joint disease. Synovial fluid obtained by arthrocentesis is often yellow, cloudy, or bloody. The joint fluid is less viscous than normal as a result of the dilution and degradation of synovial mucin by bacterial hyaluronidase and the enzymes released from the inflammatory cells within the joint. Smears of the fluid should be made for the purpose of Gram's staining and cytologic evaluation. Because it is common for synovial fluid from infected joints to clot rapidly, a portion of the fluid should be immediately placed in an anticoagulant (i.e., ethylenediaminetetraacetic acid [EDTA]) tube for future cytologic evaluation if an adequate sample is obtained. Cytologically, animals with septic arthritis show a marked increase in the number (40,000 to 280,000/µl) of nucleated cells in the synovial fluid, with neutrophils predominating (usually >90%). In very acute or severe cases it is common to see bacteria within the cells and the neutrophils may be toxic, ruptured, and degranulated. Organisms that do not cause rapid destruction of articular cartilage (i.e., streptococci, Mycoplasma) may not cause remarkable toxic or degenerative changes in synovial fluid neutrophils. In chronic infections bacteria may no longer be evident and the neutrophils may appear healthy.

Synovial fluid should be cultured for aerobic and anaerobic bacteria. A few drops of fluid should be removed from the joint and the smears stained for cytologic analysis.



**FIG 74-2 (A)** Lateral and **(B)** dorsopalmar. Radiographs of the swollen left carpus of a 2-year-old Bullmastiff with a 1-week history of lameness caused by septic arthritis. Surgical exploration revealed two porcupine quills within the infected joint.

A larger sample should then be obtained from an affected joint for culture. Direct bacterial culture of the synovial fluid is positive in approximately half of all animals with septic arthritis; improved diagnostic yield may be obtained by inoculating synovial fluid into blood culture medium (9:1 ratio) and incubating it for 24 hours at 37° C before inoculation. Bacteria can also be recovered from cultures of synovial membrane biopsy, blood, or urine specimens.

Radiographic changes of the involved joints in septic arthritis may be minimal or nonspecific initially and limited to thickening of the joint capsule, widening of the joint space, and irregular thickening of periarticular soft tissues (Fig. 74-2). In chronic infections cartilage degeneration, periarticular new bone formation, a marked periosteal reaction, and subchondral bone lysis may be seen (Fig. 74-3).

If septic arthritis is suspected and the animal has no history of direct inoculation of the joint with bacteria, a septic site in the body should be sought. Radiography of the thorax, abdomen, and spine and cardiac and abdominal ultrasonography are especially helpful in identifying a focal site of infection. If possible, cultures of material from any suspected site of infection should be performed.

#### **Treatment**

The goals of therapy are to rapidly resolve the bacterial infection and remove intraarticular accumulations of enzymes and fibrin debris. Identifiable systemic sources of infection should also be eliminated. Antibiotics should be administered as soon as possible after all samples are collected in an animal suspected of having septic arthritis. Until culture results are available, a broad-spectrum, 1-lactamaseresistant antibiotic such as a first-generation cephalosporin (e.g., cephalexin, 20 to 40 mg/kg q8h) or clavamox (Smith Kline-Beecham Animal Health; 12 to 25 mg/kg q8h) is indicated. Initially, the antibiotic can be administered parenterally, followed by long-term oral administration. Quinolones should be used if gram-negative organisms are suspected, and metronidazole should be added if anaerobic infection is suspected. Animals with acute septic arthritis can be treated conservatively initially with joint drainage and systemic antibiotics; however, if dramatic improvement is not seen within 3 days, surgery should be performed. Chronic infections, suspected intraarticular foreign bodies, postoperative joint infections, and infection in immature animals with open growth plates should all be treated with immediate surgical debridement and lavage. A minimum of 6 weeks of antibi-



A, A Very swollen elbow in a Husky-cross dog with a 3-month history of a nonweightbearing lameness not responding to antibiotics. B, Radiographs reveal marked swelling within the joint and diffuse periosteal proliferation. Synovial fluid showed septic inflammation, and surgical exploration revealed a single porcupine quill within the joint. The dog recovered completely.

otic therapy is administered, and cage rest is recommended to facilitate healing of articular cartilage.

#### **Prognosis**

The prognosis for a return to normal function depends on the severity of the damage to the articular cartilage at the time the infection is brought under control. Secondary DJD commonly occurs.

#### **MYCOPLASMA POLYARTHRITIS**

Mycoplasma spp. are normal inhabitants of the upper respiratory and urogenital tracts of most species and are generally considered nonpathogenic. Systemic Mycoplasma infection may occasionally occur in debilitated or immunosuppressed animals, but the prevalence of Mycoplasma arthritis is low. Mycoplasma gatea and Mycoplasma felis are the two organisms that have been associated with polyarthritis and tenosynovitis in cats.

Mycoplasma polyarthritis results in a chronic polyarthritis indistinguishable from idiopathic immune-mediated, nonerosive polyarthritis. Clinical signs include lameness, joint pain, depression, and fever. Synovial fluid analysis reveals an increased nucleated cell count consisting predominantly of nondegenerate neutrophils. Routine aerobic and anaerobic cultures of joint fluid are negative because Mycoplasma organisms are deficient in cell walls and cannot revert to a

parental state. Definitive diagnosis requires the isolation of organisms from synovial fluid cultured in special Mycoplasma medium. Idiopathic immune-mediated joint disease is very rare in cats, so empirical treatment with oral doxycycline (5 to 10 mg/kg q12h) for 3 weeks may be recommended in all cats with polyarthritis. Cats with polyarthritis should also be tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), and radiographs should be taken of the affected joints to look for erosive changes suggesting chronic progressive polyarthritis (see p. 1140).

#### BACTERIAL L FORM-ASSOCIATED ARTHRITIS

A rare syndrome of pyogenic subcutaneous (SC) abscesses with associated polyarthritis has been observed in cats. This syndrome appears to be infectious in nature and transmitted from one cat to another by bite wounds. No age or gender predilection exists. A bacterial L-form mutant bacteria that has lost its cell wall but can revert to its original form has been implicated. Affected cats have swollen, painful joints and fever. Fistulating SC wounds develop over the affected joints. Exudate from the joints or the SC abscesses contains degenerate and nondegenerate neutrophils and macrophages. Cultures for aerobic and anaerobic bacteria, Mycoplasma, and fungal organisms are all negative. Specific L-form media must be used to grow the organism. Radiographically, severely affected joints show extensive soft tissue swelling, periosteal proliferation, and destruction of articular cartilage and subchondral bone, resulting in subluxation and joint space collapse. Electron microscopic studies and antibiotic sensitivity testing can yield findings that help support a diagnosis of L-form bacterial infection. Rarely, cats are concurrently infected with FeIV or FIV. Treatment with doxycycline (5 mg/kg q12h) or chloramphenicol (10 to 15 mg/kg q12h) is effective, with improvement noted within 48 hours. Therapy should continue for 10 to 14 days.

#### RICKETTSIAL POLYARTHRITIS

Nonerosive polyarthritis has been recognized in association with several tick-borne rickettsial diseases, including Rocky Mountain spotted fever (RMSF) caused by Rickettsia rickettsii, canine monocytic ehrlichiosis caused by Ehrlichia canis, and canine granulocytic anaplasmosis (GA) caused by Anaplasma phagocytophilium (formerly Ehrlichia equi). The polyarthritis in these disorders may be related to immune complex deposition in the joints. Most infected dogs have other systemic signs of illness (see Chapter 96). Joint pain and effusion are noted, and increased numbers of nondegenerate neutrophils are identified in the joint fluid; occasionally, Ehrlichia or Anaplasma morulae can be identified in cytologic preparations of joint fluid. Fever and polyarthritis may be the only clinical abnormalities in dogs with ehrlichiosis and anaplasmosis, although hematologic abnormalities such as thrombocytopenia and anemia are common. Serologic testing for Ehrlichia canis and Anaplasma phagocytophilium is widely available, but positive results merely indicate prior exposure and do not necessarily indicate active infection.

Dogs with polyarthritis caused by RMSF are more likely to show a variety of clinical signs resulting from widespread vasculitis, including fever, petechiae, lymphadenopathy, neurologic signs, edema of the face or extremities, and pneumonitis. Hematologic abnormalities, including thrombocytopenia, are common. Diagnosis is made on the basis of the results of serologic testing and demonstration of a fourfold increase in serum IgG concentrations over 2 to 3 weeks (see Chapter 96).

Acute rickettsial infections causing polyarthritis are best treated with oral doxycycline (5 mg/kg q12h). Empirical antibiotic treatment is warranted in all dogs from endemic areas with confirmed polyarthritis, especially if there is concurrent thrombocytopenia or other evidence of rickettsial infection. Concurrent glucocorticoid therapy (prednisone, 0.5 to 2.0 mg/kg PO q24h) may be necessary in some dogs with confirmed rickettsial polyarthritis if antimicrobial therapy alone does not eliminate the fever, lameness, and joint swelling. Antibiotic treatment should continue for at least 3 weeks.

#### LYME DISEASE

#### Etiology

Infection by the tick-borne spirochete Borrelia burgdorferi (Bb) can cause illness (Lyme disease) in dogs. Ticks of the

genus *Ixodes* transmit the spirochete, requiring at least 50 hours of tick attachment for transmission. Although serologic evidence of exposure is common in dogs throughout North America, most reports of canine Lyme disease have occurred in dogs from the northeastern and mid-Atlantic states, with Minnesota, Wisconsin, California, and Oregon accounting for most of the remaining cases.

#### **Clinical Features**

Most dogs bitten by ticks infected with Bb never develop clinical signs of illness. Experimentally infected healthy adult dogs remain asymptomatic, while 6- to 12-week-old puppies develop self-limiting, often recurrent polyarthritis. Acute polyarthritis is the most common form of Lyme borreliosis diagnosed in naturally infected dogs. Clinical features of Lyme polyarthritis include shifting leg lameness, joint swelling, fever, lymphadenopathy, and anorexia. Cytologic examination of synovial fluid reveals neutrophilic inflammation. Cardiac, renal, and neurologic manifestations (e.g., seizure, behavior change) have also been attributed to Bb infection in dogs. There are numerous reports of dogs with Bb antibody developing a unique progressive renal disorder characterized by immune-mediated glomerulonephritis, tubular necrosis, and lymphocytic-plasmacytic interstitial nephritis. This disorder is most common in Labrador and Golden Retrievers, resulting in uremia, proteinuria, peripheral edema, body cavity effusions, and death. Because of the high rate of seropositivity in endemic areas and the frequency of concurrent infection with other tick-borne diseases, it is difficult to determine how common Lyme disease is in clinical practice. The rate of veterinary diagnosis of canine Lyme polyarthritis certainly far exceeds its actual prevalence.

#### Diagnosis

Lyme disease should be suspected in dogs from endemic areas with fever, lameness, and anorexia. Synovial fluid analysis confirms polyarthritis. Attempts to culture Bb from the blood, urine, and synovial fluid of affected dogs are usually unsuccessful. Lyme disease polyarthritis should be diagnosed only if the animal has a history of recent potential exposure, the synovial fluid is confirmed to be inflammatory and sterile, serologic testing is positive, infection with other tickborne diseases is eliminated, and a prompt and permanent response to appropriate antibiotic therapy is seen. The diagnosis can be supported by the identification of *Borrelia* organisms in biopsy specimens of tissues prepared using special stains and monoclonal antibodies.

#### **Treatment**

Antibiotics are the treatment of choice. Doxycycline (5 mg/kg, administered orally q12h), amoxicillin (22 mg/kg, administered orally q12h), ampicillin (22 mg/kg, administered orally q8h), Clavamox (12.5 to 25 mg/kg, administered orally q8-12h), and Cephalexin (20 to 40 mg/kg, administered orally q8h) are all effective. Treatment during the acute stage of the disease should result in rapid clinical improvement (i.e., within 2 to 3 days). Treatment for at least 4 weeks is advised.

Failure to recognize acute disease or the institution of inappropriate treatment can allow chronic disease to develop, including relapsing polyarthritis, glomerulonephritis, and cardiac abnormalities.

#### **Prevention**

The prevention of Lyme disease is discussed in Chapter 69.

#### **LEISHMANIASIS**

Leishmaniasis is a chronic systemic disease caused by a protozoan parasite found mainly in Central and South America and in Africa, India, and the Mediterranean. In the United States *Leishmania* spp. are endemic in Ohio, Oklahoma, and Texas. Clinical abnormalities develop 3 months to 7 years after infection and typically consist of vague signs, including weight loss, lymphadenopathy, and splenomegaly. Hyperglobulinemia, hypoalbuminemia, and proteinuria are expected. Polyarthritis causing lameness and exercise intolerance is common. Many affected dogs will have erosive disease, with radiographic evidence of periarticular lysis and periosteal proliferation. Diagnosis is made when organisms are identified within macrophages in lymph node or splenic aspirates or in joint fluid (see Chapter 94).

#### **FUNGAL ARTHRITIS**

Fungal infection of the joints is very rare. When it does occur, it is usually as an extension of fungal osteomyelitis caused by *Coccidioides immitis, Blastomyces dermatitidis*, or *Cryptococcus neoformans*. More commonly a reactive, immunologically mediated, culture-negative polyarthritis occurs in dogs and cats with systemic fungal infections.

## VIRAL ARTHRITIS Calicivirus

Natural calicivirus infection and attenuated live calicivirus vaccination have been associated with the development of transient polyarthritis in 6- to 12-week-old kittens. Clinical signs include lameness, stiffness, and fever, which usually resolve spontaneously after 2 to 4 days (Fig. 74-4). Some kittens go on to develop overt calicivirus infection, with glossal and palatine vesicles or ulcers and signs of upper respiratory tract disease. Synovial fluid analysis reveals a mildly to greatly increased nucleated cell count, with small mononuclear cells and macrophages predominating, some of which contain phagocytosed neutrophils. Two specific strains of calicivirus have been implicated. Isolation of the virus from affected joints has been unrewarding, although the virus can be found in the oropharynx of some infected cats.

## NONINFECTIOUS POLYARTHRITIS: NONEROSIVE

Noninfectious inflammatory joint diseases are very common in the dog and rare in the cat. These immune-mediated polyarthritis syndromes are routinely classified as being



FIG 74-4
Presumed calicivirus polyarthritis in a 10-week-old kitten exhibiting swollen joints, lameness, and fever 6 days after modified-live virus vaccination.

erosive or nonerosive on the basis of the presence or absence of radiographically evident joint destruction. Erosive disorders are very rare, consisting of fewer than 1% of canine polyarthritis cases. The nonerosive immune-mediated polyarthritis (IMPA) syndromes are all thought to be mediated through immune complex formation and deposition. Immune-mediated nonerosive polyarthritis occurs as a feature of systemic lupus erythematosus (SLE), secondary to antigenic stimulation from chronic infection, neoplasia, or drugs (i.e., reactive polyarthritis), or as an idiopathic syndrome. Breed-associated syndromes of polyarthritis or polyarthritis/meningitis or polyarthritis/myositis also exist and are thought to have a genetic basis.

#### SYSTEMIC LUPUS ERYTHEMATOSUS-INDUCED POLYARTHRITIS

SLE is a condition in which autoantibodies against tissue proteins and DNA result in circulating immune complexes that, when deposited in tissues, induce inflammation and organ damage (see Chapter 104). German Shepherd Dogs may be predisposed, but any breed of dog may be affected. SLE is most commonly diagnosed in dogs 2 to 4 years old. Criteria for SLE diagnosis vary between studies, but SLE is considered to be the cause of fewer than 20% of all cases of immune-mediated nonerosive polyarthritis in dogs. Although SLE is a relatively uncommon cause of polyarthritis in dogs compared with idiopathic immune-mediated polyarthritis, its effects on other organ systems can be devastating, which makes accurate diagnosis important.

#### **Clinical Features**

The clinical manifestations of SLE vary with the organ involved and include intermittent fevers, polyarthritis, glomerulonephritis, skin lesions, hemolytic anemia, immunemediated thrombocytopenia, myositis, and polyneuritis. Polyarthritis is the most common manifestation, occurring in 70% to 90% of dogs diagnosed with SLE. Some affected dogs show no signs referable to their joint disease, and polyarthritis is detected when synovial fluid is examined as part of a workup for fever, inflammatory clinicopathologic tests, or polysystemic immune-medicated disease. More often, dogs with SLE polyarthritis show generalized stiffness, joint swelling, or a shifting leg lameness. SLE causes a sterile, nonerosive polyarthritis, with distal joints (i.e., hocks, carpi) usually more severely affected than proximal joints. Synovial fluid analysis reveals an increased white blood cell count (5000 to 350,000/ml) consisting primarily of nondegenerate neutrophils (>80%). In rare instances, lupus erythematosus (LE) cells are detected in the synovial fluid (see Fig. 73-9).

#### Diagnosis

SLE should be considered in any dog with non-infectious polyarthritis. A complete blood count (CBC), platelet count, biochemistry profile, urinalysis, urine protein : creatinine ratio determination, and careful physical examination should be performed to search for other manifestations of this disease. Laboratory tests that may aid in the diagnosis of SLE polyarthritis include the LE cell test (positive in 30% to 90% of cases) and the antinuclear antibody (ANA) test (positive in 55% to 90% of cases). An animal may be said to have SLE if one or more of these "specific" diagnostic tests (e.g., ANA, LE) are positive and the animal has two or more of the clinical abnormalities known to be associated with SLE (e.g., polyarthritis, glomerulonephritis, anemia, thrombocytopenia, dermatitis; see Chapter 104). When two or more of the common clinical syndromes are recognized but none of the serologic tests are positive, the dog is determined to have an SLE-like multisystemic immune-mediated disease.

#### **Treatment**

Treatment for SLE-associated polyarthritis is the same as that used for idiopathic, immune-mediated polyarthritis (Chapter 74). If the animal is clinically normal and synovial fluid is non-inflammatory after 6 months of therapy, it may be worthwhile to discontinue medications because long periods of drug-free remission can occur.

#### **Prognosis**

The prognosis is good from the standpoint of controlling the polyarthritis, but multisystemic involvement (particularly glomerulonephritis) may progress despite therapy, occasionally resulting in death.

#### REACTIVE POLYARTHRITIS

Reactive polyarthritis accounts for approximately 25% of all nonerosive immune-mediated polyarthritis cases. Reactive polyarthritis is most often seen in association with chronic bacterial, fungal, or rickettsial infections; neoplasia; or drug administration. Reactive polyarthritis has been documented in dogs with endocarditis, foreign body abscesses or granulomas, diskospondylitis, heartworm disease, pancreatitis, pro-



FIG 74-5

A 2-year-old German Shepherd Dog/Labrador Retriever cross with reactive polyarthritis (A). The dog was seen because of a 3-month history of shifting leg lameness and weight loss. There was joint swelling and pain and a grade IV/VI diastolic cardiac murmur. Synovial fluid was inflamed but sterile. A cardiac ultrasound study suggested infective endocarditis of the aortic valve, which was confirmed by postmortem evaluation (B).

statitis, pyelonephritis, pneumonia, other chronic infections, and a variety of tumors (Fig. 74-5). Drugs that have been implicated in causing reactive polyarthritis include sulfadiazine-trimethoprim, phenobarbital, erythropoietin, penicillin, cephalexin, and routine vaccinations. Rarely, gastrointestinal disorders such as inflammatory bowel disease, salmonellosis, and chronic active hepatitis have also been associated with reactive polyarthritis.

Because many animals with reactive polyarthritis have vague or minimal clinical signs referable to their underlying disease, they will be presented for veterinary evaluation when their joint inflammation makes them reluctant to walk. Therefore it is important to perform a thorough physical examination of every animal with polyarthritis and to obtain a complete history regarding the administration of medications and the presence or absence of systemic signs. Once infectious causes of polyarthritis have been eliminated, screening tests (i.e., CBC, biochemical panel, urinalysis, thoracic and abdominal radiography, abdominal ultrasonogra-

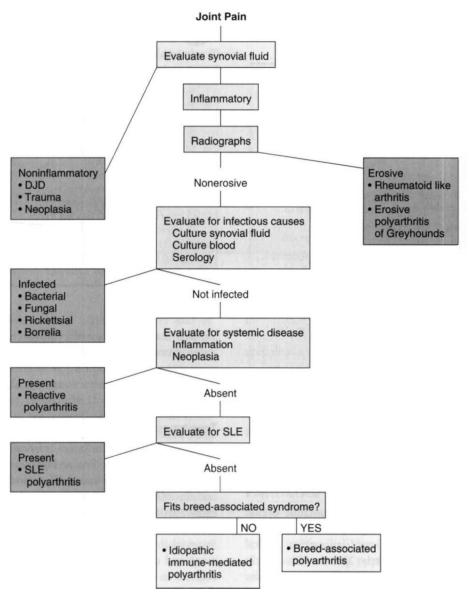


FIG 74-6
Algorithm for diagnostic evaluation of dogs with joint pain.

phy, culture of urine and blood, lymph node aspirates, cardiac ultrasonography) may be required to identify underlying chronic infections or neoplasia (Fig. 74-6).

Clinical signs in dogs with reactive polyarthritis typically include cyclic fevers, stiffness, and lameness. Synovial fluid analysis reveals an increase in the WBC count and the percentage of neutrophils in affected joints, but synovial fluid culture is negative. Even if the underlying inflammatory disease is infectious, the polyarthritis in these patients is caused by synovial deposition of circulating immune complexes, not by infection of the joints. Radiographically, the only finding is joint swelling.

Treatment must be directed at eliminating the underlying disease or antigenic stimulus using medications or surgery whenever possible. If this can be done, the polyarthritis usually resolves without additional therapy. Short-term, low-

dose corticosteroid therapy (prednisone, 0.25 to 1.0 mg/kg q24h) or NSAID therapy may be warranted to control the synovitis in severe cases.

## IDIOPATHIC, IMMUNE-MEDIATED, NONEROSIVE POLYARTHRITIS

Nonerosive, noninfectious polyarthritis in which a primary or underlying disease cannot be identified is referred to as *idiopathic immune-mediated polyarthritis (IMPA)*. This disorder can be diagnosed only by ruling out the other causes of polyarthritis, but it is the most common form of polyarthritis diagnosed in dogs (Box 74-1). It is especially common in sporting and large breeds. Dogs of any age can be affected, but the incidence peaks at 2.5 to 4.5 years. Idiopathic, immune-mediated, nonerosive polyarthritis is uncommon in cats.



BOX 74-1

Classification of Polyarthritis in Dogs

#### Infectious

**Bacterial** Mycoplasma Rickettsial Lyme borreliosis Leishmaniasis Fungal Viral

#### Noninfectious, Nonerosive

Idiopathic, immune-mediated polyarthritis Systemic lupus erythematosus Reactive polyarthritis (bacterial, fungal, parasitic, neoplastic, enterohepatic, drug reaction, vaccine induced) Breed-associated syndromes Polyarthritis (Akita, Newfoundland, Weimaraner) Polyarthritis/meningitis (Akita, Beagle, Bernese Mountain Dog, Boxer, German Shorthair Pointer) Polyarthritis/polymyositis (Spaniels) Familial Shar-Pei fever

#### Noninfectious, Erosive

lymphoplasmacytic synovitis

Rheumatoid-like arthritis Erosive polyarthritis of Greyhounds

#### **Clinical Features**

The clinical signs of idiopathic IMPA may include cyclic fevers, stiffness, and lameness. Multiple joints are usually involved, with the small distal joints (i.e., carpus, hock) affected most severely. Approximately 20% to 50% of all affected dogs may not have palpable joint effusion or localizable pain. Cervical pain and vertebral hypersensitivity are common complaints, reflecting either intervertebral facetal joint involvement or the presence of concurrent steroid-responsive meningitis-arteritis (see Chapter 69). Some dogs are evaluated because of a vague history of decreased appetite or because of fever of unknown origin.

#### Diagnosis

Idiopathic IMPA is diagnosed on the basis of the results of synovial fluid analysis, failure to identify an infectious cause, and the absence of evidence to support a diagnosis of SLE or reason to suspect reactive polyarthritis (Fig. 74-6). A CBC typically reveals neutrophilia, although some dogs have a normal CBC. Hyperglobulinemia and hypoalbuminemia are common, reflecting ongoing systemic inflammation. When radiographs are taken, the findings are normal or limited to joint and periarticular swelling with no bone or cartilage abnormalities. Synovial fluid is thin and may be turbid. Nucleated cell counts are increased (4000 to 370,000 cells/ µl), and nondegenerate neutrophils predominate (usually >80%). In animals with less severe or fluctuating disease and



Treatment Recommendations for Idiopathic Immune-Mediated Polyarthritis

- Prednisone 2 mg/kg q12h orally for 3-4 days
- 2. Prednisone 2mg/kg q24h orally for 14 days
- 3. Assess clinical response and synovial fluid cytology If clinical signs have resolved, the dose of prednisone is gradually tapered, evaluating clinical response and synovial fluid before each dose reduction.
- 1 mg/kg q24h ×4 weeks
- 1 mg/kg q48h ×4 weeks
- 0.5 mg/kg q48h ×4 weeks 0.25 mg/kg q48h ×8 weeks
- If clinical signs of joint inflammation are present at any recheck, return to step 2 and add azathioprine (2 mg/kg/day) to treatment. Continue prednisone taper after signs resolve and synovial fluid is normal.

animals that have received corticosteroids, there may be a lower synovial fluid white blood cell count and a lower percentage of neutrophils (15% to 80%). Blood, urine, and synovial fluid cultures are negative for bacteria and Mycoplasma spp.

#### **Treatment**

Glucocorticoids are the initial treatment of choice for dogs with idiopathic IMPA. Prednisone treatment alone results in remission in 50% of cases. Immunosuppressive doses are initially administered, and the dosage is gradually decreased every 3 to 4 weeks if the animal is clinically normal and the inflammation in the synovial fluid has subsided (Box 74-2). Synovial fluid should be monitored carefully during treatment and determined to be noninflammatory before each decrease in drug dose. If the joints are not inflamed, the drug doses may be slowly tapered. If a dog can be maintained on a low, alternate-day dose of prednisone (0.25 mg/kg q48h) for 2 months and the synovial fluid is not inflammatory, it should be possible to discontinue all therapy. Approximately 50% of affected dogs will need at least alternate-day lowdose prednisone therapy for the remainder of their lives. In dogs receiving a stable dose of medication, synovial fluid should be evaluated every 4 to 6 months.

Azathioprine (Imuran; Burroughs Wellcome) should be administered to dogs with persistent inflammation of synovial fluid despite prednisone therapy and to dogs that cannot be tapered to a low dose of prednisone without relapse. Azathioprine may also be used from the beginning in dogs that do not tolerate prednisone therapy. Azathioprine (2.2 mg/kg) is administered once daily for 4 to 6 weeks and then only on alternate days if the animal is doing well clinically and the synovial fluid is no longer inflammatory. Some dogs will require lifelong azathioprine therapy. In most dogs azathioprine is well tolerated, with myelosuppression its major toxicity. A CBC and platelet count should be performed initially every 2 weeks and then every 6 to 8 weeks



#### Drugs Used in the Treatment of Immune-Mediated Polyarthritis

DRUG	DOSAGE						
Prednisone	Variable						
Azathioprine (Imuran, GlaxoSmithKline)	2.2 mg/kg PO q24-48h						
Cyclosporine (Neoral, Novartis)	2.5 mg/kg PO q12 h						
	Target blood level 400 ng/ml						
Leflunomide (Arava, Aventis Pharma)	4 mg/kg q24h						
	Target trough blood level 20 µg/ml						
Gold salt injections (Solganol, Shering)	0.5-1.0 mg/kg weekly IM for 8 weeks, then monthly						
Cyclophosphamide (Cytoxan, Bristol-Myers-Squibb	50 mg/M <sup>2</sup> PO q48h						
Chlorambucil (Leukeran, GlaxoSmithKline)	2 mg/M <sup>2</sup> PO q48h						
Methotrexate (Rheumatrex, Lederle)	2.5 mg/M <sup>2</sup> PO q48h						

PO, oral; IM, intramuscular.

during therapy. Hepatic enzyme activities should also be monitored to facilitate the early detection of hepatotoxicity. Dogs treated with azathioprine and prednisone may also be at increased risk for developing pancreatitis.

Additional immunosuppressive agents are rarely necessary because idiopathic, nonerosive IMPA is easy to control in most patients. If the polyarthritis is refractory to treatment, the patient should be reevaluated for infectious disease, reactive polyarthritis, and erosive disease. When necessary, other immunosuppressive agents can be administered (Table 74-2). In addition to medical treatment, management should initially include restricted exercise, followed by regular gentle exercise and weight control. Chondroprotective agents, omega-3 fatty acids, and antioxidants may also prove beneficial. (See Chapter 103 for more information on immunosuppressive treatment.)

#### **Prognosis**

The prognosis for animals with idiopathic, immunemediated, nonerosive polyarthritis is good. One dog in 50 is very difficult to treat and keep in remission. Dogs that require long-term (4 to 5 years) high-dose immunosuppressive drug therapy for this disorder may develop symptomatic DJD secondary to chronic low-grade synovial inflammation or the detrimental effects of corticosteroids on cartilage synthesis and repair.

#### **BREED-SPECIFIC POLYARTHRITIS SYNDROMES**

Immune-mediated polyarthritis has been shown to be a problem in a number of breeds. A heritable polyarthritis has been documented in Akitas younger than 1 year of age and sporadically in Newfoundlands and Weimaraners. Many of these dogs have a concurrent meningitis resembling the meningeal vasculitis syndromes seen in a few other breeds (see Chapter 69). ANA tests are negative in these animals, and generally they respond poorly to immunosuppressive therapy. In contrast, polyarthritis that accompanies meningeal vasculitis in some Boxers, Bernese Mountain dogs, German Shorthair Pointers, and Beagles often responds completely to immunosuppressive therapy.

Familial polyarthritis with concurrent myositis has been rarely reported in a few Spaniel breeds. Affected dogs are exercise intolerant and exhibit a crouched stance at rest. Widespread muscle atrophy is common, occasionally leading to muscle fibrosis, contracture, and reduced mobility. Muscle enzymes (CK, AST) may be increased. Response to therapy is often poor.

#### FAMILIAL CHINESE SHAR-PEI FEVER

A disorder characterized by recurrent fevers and periarticular swelling has been documented in the Shar-Pei and is known as "familial Shar-Pei fever" (FSF) or "Sharpei hock" syndrome. Growing pups or young adult dogs are initially affected by episodes of fever lasting 24 to 36 hours. Approximately 50% of affected dogs develop swelling of the tissues around the hock joint during the febrile episodes, and a few dogs develop polyarthritis. Affected dogs are at increased risk for systemic amyloidosis, leading to renal or hepatic failure. Renal amyloid deposition is primarily medullary, and not all dogs will exhibit proteinuria. Hyperglobulinemia and increased serum concentrations of the cytokine interleukin-6 are common. Glomerulonephritis, pyelonephritis, renal infarcts, and systemic thromboembolic disease may occur. This disorder is inherited as an autosomal trait. Treatment is symptomatic to control the fevers and inflammation. Oral administration of colchicine (0.03 mg/kg q24h) may decrease amyloid deposition.

#### LYMPHOPLASMACYTIC SYNOVITIS

Lymphoplasmacytic synovitis is present in some dogs with partial and complete tears of the cranial cruciate ligament, but the relationship between the immune-mediated response and the ligament rupture is uncertain. Partial tears or ruptures of the cruciate ligament commonly initiate an inflammatory reaction directed against the collagen of the ligament, resulting in mildly inflammatory synovial fluid and synovial fluid antibodies directed against type 1 and type 2 collagen. An alternative theory is that lymphoplasmacytic synovitis is a primary immune-mediated disorder that causes joint laxity and instability, eventually leading to rupture of the cranial cruciate ligament. Some investigators have estimated that perhaps as many as 10% to 25% of cruciate ruptures in dogs are caused by this immunologic disorder, but this is a controversial claim.

Dogs diagnosed with lymphoplasmacytic synovitis are the same dogs typically presented for cruciate ligament rupture, with Rottweilers, Newfoundlands, Staffordshire Bull Terriers, and Labrador Retrievers most commonly affected. Clinical signs are limited to acute or chronic lameness involving one or both stifles. Cruciate ligament rupture at the time of diagnosis may be partial or complete and not usually historically associated with trauma. Arthroscopy or magnetic resonance imaging (MRI) may be required to confirm the diagnosis of partial rupture. Affected animals are in good body condition and are not systemically ill; CBC is normal. Synovial fluid is thin and turbid, with an increased nucleated cell count (5000 to 20,000 cells/1 l, but occasionally >200,000/11). Lymphocytes and plasma cells predominate (60% to 90%) in the synovial fluid. Characteristic histopathologic changes in the synovial lining include lymphocytic and plasmacytic infiltration and villous hyperplasia. Biopsy of ligament and synovium should be performed at the time of surgical exploration and repair in all dogs with nontraumatic cruciate ligament ruptures. Surgical stabilization of the stifle and treatment with NSAIDs usually results in rapid resolution of clinical signs. Some dogs will have persistent effusion and discomfort that responds well to immunosuppressive treatment with prednisone and/or azathioprine, initiated a minimum of 3 days after NSAID therapy is discontinued.

## NONINFECTIOUS POLYARTHRITIS: EROSIVE

## CANINE RHEUMATOID-LIKE POLYARTHRITIS

A disorder resembling human rheumatoid arthritis (RA) rarely results in erosive polyarthritis and progressive joint destruction in dogs. Small and toy breeds are most commonly affected. The age of onset is variable (i.e., 9 months to 13 years), but most affected dogs are young or middle-aged. Initially, the disease is indistinguishable from idiopathic nonerosive polyarthritis, but the joints are destroyed over time (weeks to months), with distal joints most severely affected.

#### Etiology

The pathogenesis of canine RA-like polyarthritis is poorly understood. Antibodies directed against immunoglobulin G (i.e., rheumatoid factors [RF]) form and complex with IgG within the synovium. This results in complement activation

and the chemotactic attraction of plasma cells, lymphocytes and neutrophils into the joint fluid. The synovial membrane thickens and develops a fibrous, vascular granulation tissue (pannus), which invades articular cartilage, tendons, ligaments, and subchondral bone. Proteolytic enzymes are released that erode the articular cartilage and the subchondral bone, leading to joint collapse and the radiographically visible "punched-out" subchondral bone lesions. Articular and periarticular inflammation and instability lead to joint subluxation and luxation, resulting in joint deformity.

#### **Clinical Features**

Affected dogs initially have signs indistinguishable from those of other forms of polyarthritis. A low-grade fever, depression, anorexia, and reluctance to exercise are common. Joint-related clinical signs such as joint pain and stiff gait are prominent. Signs may be sporadic initially, and stiffness is generally worse after rest and improves with mild exercise. The joints may appear normal or be swollen and painful. The joints most commonly affected are the carpi, hocks, and phalanges, although elbows, shoulders, and stifles can also be affected. As the disease progresses, clinical examination reveals crepitus, laxity, luxation, and deformity of affected joints (Fig. 74-7).

Radiographic features may be subtle at the time of initial diagnosis, with intracapsular swelling the only consistent finding. Later, characteristic changes consist of focal, irregular, radiolucent, cystlike areas of subchondral bone destruction (Fig. 74-8); joint space collapse; and joint subluxation and luxation. If RA is suspected, carpi and hocks should be radiographed bilaterally.

#### Diagnosis

of Saskatchewan.)

RA-like polyarthritis should be suspected in any dog with erosive polyarthritis once infectious causes have been eliminated. The synovial fluid in affected joints is thin, cloudy,



FIG 74-7
Complete collapse of both carpi resulting in luxation and severe distortion of the forelimbs in a Dachshund with rheumatoid arthritis (RA). (Courtesy Dr. D. Haines, University



FIG 74-8
Radiographs of both carpal joints of a 9-year-old female Shih Tzu. Both carpi are severely deformed secondary to erosive rheumatoid-like polyarthritis. The intercarpal spaces have thinned laterally, and there are focal radiolucent cystlike areas of subchondral bone destruction and regional soft-tissue swelling. There is dislocation of the radius and ulna from the carpus bilaterally.

and hypercellular (6000 to 80,000 white blood cells/µl; mean, 30,000/µl). Neutrophils may be the predominant cell (20% to 95%; average 74%), or mononuclear cells may predominate. Culture of the synovial fluid is negative. Whenever possible, the synovial fluid should be collected during a period when the dog is most symptomatic because the cyclical nature of the disease occasionally makes diagnosis difficult.

Serologic tests for circulating RF are positive in 20% to 70% of affected dogs (see Chapter 73). Weak false-positive results are common in dogs with other systemic inflammatory diseases. Synovial biopsy may help to establish the diagnosis, revealing synovial thickening, hyperplasia, and proliferation with pannus formation. The pannus is composed primarily of proliferating activated synoviocytes, lymphocytes, plasma cells, macrophages, and neutrophils. Culture of the synovial biopsy is negative. RA is diagnosed on the basis of the typical clinical findings and radiographic features, characteristic synovial fluid features, a positive RF test result, and the typical histopathologic changes seen in a synovial biopsy specimen.

#### **Treatment**

Early treatment of RA is important to prevent irreversible changes and progressive disease. Medical treatment usually includes immunosuppressive drugs and chondroprotective agents. Initially, most dogs are treated with oral prednisone (2 to 4 mg/kg q24h for 14 days, then 1 to 2 mg/kg q24h for 14 days) and azathioprine (2.2 mg/kg q24h), administered as described for the treatment of refractory idiopathic, nonerosive polyarthritis. Oral chondroprotective agents (see Table 74-1) are routinely administered. Subjective improvement has also been observed in dogs receiving injectable chondroprotective agents (e.g., Adequan).

After 1 month of therapy, the dog is reexamined and synovial fluid is evaluated. If the fluid is non-inflammatory, the corticosteroid dose is decreased to 1 to 2 mg/kg orally every 48 hours and treatment with azathioprine is continued. If the fluid is still inflammatory, then daily administration of prednisone (1 to 2 mg/kg) and azathioprine (2.2 mg/kg) continues and oral methotrexate (Rheumatrex, Lederle; 2.5 mg/m<sup>2</sup> q48h) may be added to the treatment regimen. Monthly evaluation of synovial fluid is recommended. If inflammation of the synovial fluid persists after 2 months, additional therapy such as Leflunomide (Arava; Aventis Pharma), a pyrimidine synthesis inhibitor, may be added to the treatment regimen (see Table 74-2). Leflunomide is administered at an initial dose of 4 mg/kg q24h, and the dose is adjusted to maintain a trough plasma level of 20 mg/ml (the usual maintenance dose is 0.5 mg/kg q24h). (See Chapter 103 for more information on immunosuppressive treatment.)

Some therapeutic success may be expected if treatment is initiated before joint damage is severe. In most cases, however, damage to the articular cartilage is severe before the diagnosis is made. Many dogs require additional therapy with analgesics such as tramadol to control joint discomfort. RA is a relentlessly progressive disorder, and even with appropriate therapy most dogs show deterioration with time. Surgical procedures can occasionally be used to improve joint stability and pain. Synovectomy, arthroplasty, joint replacement, and arthrodesis may decrease pain and improve function.

## EROSIVE POLYARTHRITIS OF GREYHOUNDS

An erosive, immune-mediated polyarthritis occurs in Greyhounds from 3 to 30 months of age. This disorder is primarily seen in Australia and Britain. The proximal interphalangeal joints, carpi, hocks, elbows and stifles are most commonly affected. Clinical signs include generalized stiffness, joint pain or swelling, and a single or multiple limb lameness that may be intermittent. The synovial membrane is infiltrated with lymphocytes, and plasma cells and synovial fluid analysis reveals an increase in these same cells. There is extensive necrosis of deep articular cartilage zones, with relative sparing of the superficial surface cartilage. Therapy is as for refractory idiopathic, immune-mediated, nonerosive polyarthritis: administering prednisone, azathioprine, and chondroprotective agents. Response to treatment is variable.

## FELINE CHRONIC PROGRESSIVE POLYARTHRITIS

An uncommon syndrome of erosive polyarthritis has been reported in cats. This disorder affects primarily intact and castrated male cats, and the onset of signs is usually between 1.5 and 4 years of age, although older cats are occasionally affected. The pathogenesis of the disorder is not well understood, but all affected cats are infected with FeSFV (feline syncytium-forming virus) and approximately 60% are infected with FeLV or FIV or both. Two clinical variants of this disorder affect cats: (1) a proliferative periosteal form and (2) a more severe, deforming erosive arthritis that resembles RA.

The periosteal proliferative form is most common and is characterized by the acute onset of fever, stiff gait, joint pain, lymphadenopathy, and edema of the skin and soft tissues overlying the joint. Synovial fluid analysis initially reveals inflammation with an increased white blood cell count, particularly neutrophils. As the disease becomes chronic, the proportion of lymphocytes and plasma cells increase. Initially, the radiographic changes are mild and include periarticular soft tissue swelling and mild periosteal proliferation. With time, the periosteal proliferation worsens and periarticular osteophytes, subchondral cysts, and collapse of the joint space may be noted.

The deforming type of chronic progressive polyarthritis is rare and has an insidious onset, with the slow development of lameness and stiffness. Deformation of the carpal and distal joints is common. Severe subchondral central and marginal erosions, luxations, and subluxations can be seen radiographically, which can lead to joint instability and deformities. Cytologic findings in synovial fluid are less remarkable than those in the periosteal proliferative form and consist of a mild to moderate increase in inflammatory cells (i.e., neutrophils, lymphocytes, macrophages).

#### Diagnosis

The diagnosis is based on the typical signalment, clinical signs, radiographic features, and results of synovial fluid

analysis. Tests for FeSFV (when available) and FeLV may be positive. In addition, cultures of synovial fluid are negative, and no evidence of an underlying disorder causing a reactive polyarthritis is seen.

#### **Treatment**

Treatment with prednisone (4 to 6 mg/kg/day) may slow the progression of these diseases. If the cat shows clinical improvement after 2 weeks, the dose of prednisone can be decreased to 2 mg/kg daily. Long-term alternate-day prednisone therapy (2 mg/kg q48h) may be adequate in some cats. Combination therapy with chlorambucil (Leukeran; Burroughs Wellcome; 20 mg/m², administered orally every 2 weeks) may aid in long-term control. Concurrent treatment with analgesics such as amantadine (3 mg/kg, administered orally q24h), amitryptyline (0.5-2.0 mg/kg, administered orally q24h), or gabapentin (2-10 mg/kg, administered orally q24h) may make affected cats more comfortable. Although many cats respond initially to therapy, the prognosis for adequate long-term control is poor, and most affected cats are euthanized.

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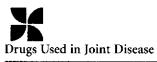
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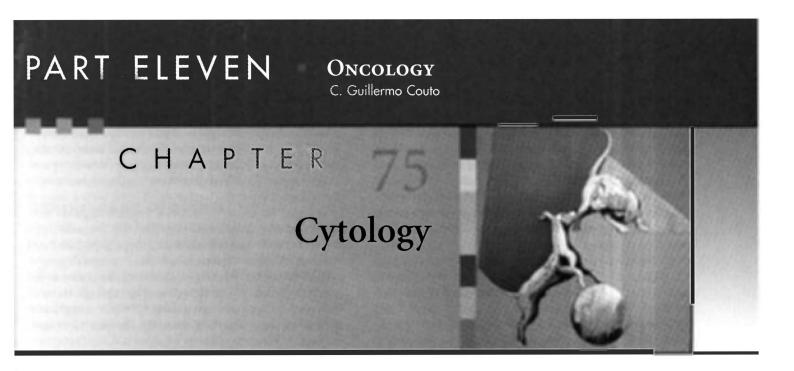
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		RECOMMENDED DOSE				
DRUG NAME (TRADE NAME)	PURPOSE	DOG	CAT			
Acetylsalicylic acid (aspirin)	Analgesia, antiinflammatory	10-20 mg/kg PO q8h	10 mg/kg PO q48h			
Amantadine	Analgesic	3 mg/kg PO q24h	same			
Amoxicillin	Antibiotic	22 mg/kg PO q12h	same			
Amoxicillin with clavulanic acid (Clavamox)	Antibiotic	12-25 mg/kg PO q8h	same			
Ampicillin	Antibiotic	22 mg/kg PO q8h or 22 mg/kg IV, SC, IM q6h	same			
Azathioprine (Imuran)	Immunosuppression	2.2 mg/kg PO q24-48h	none			
Carprofen (Rimadyl)	Analgesia, antiinflammatory	2.2 mg/kg PO q12h	none			
Cefotaxime	Antibiotic	20-40 mg/kg IV q6h	same			
Ceftriaxone	Antibiotic	25 mg/kg IV or SC q24h	same			
Cephalexin (Keflex)	Antibiotic	20-40 mg/kg PO q8h	same			
Chlorambucil (Leukeran)	Immunosuppression	2 mg/M² PO q48h				
Chondroitin sulfate	Chondroprotective	15-20 mg/kg PO q12h	same			
Colchicine	Antiinflammatory	0.03 mg/kg PO q24h	same			
Cyclophosphamide (Cytoxan)	Immunosuppression	50 mg/M <sup>2</sup> PO q48h	same			
Cyclosporine (Neoral)	Immunosuppression	2.5 mg/kg PO q12h	same			
Deracoxib (Deramaxx)	Analgesia Antiinflammatory	1-2 mg/kg PO q24h	none			
Doxycycline	Antibiotic	5-10 mg/kg PO, IV q12h	same			
Enrofloxacin (Baytril)	Antibiotic	5 mg/kg PO, SC, IV q12h	5 mg/kg PO or IM q12h			
Etodolac (Etogesic)	Analgesia, antiinflammatory	10-15 mg/kg PO q24h	none			
Firocoxib (Previcox)	Analgesia, antiinflammatory	5 mg/kg PO q24h	none			
Gabapentin (Neurontin)	Analgesia	5-20 mg/kg PO q8-12h	2-10 mg/kg PO q24h			
Glucosamine	Chondroprotective	15-20 mg/kg PO q12h	same			
Gold Salt injections (Solganol)	Immunosuppression	0.5-1.0 mg/kg IM q7d	same			
Leflunomide (Arava)	lmmunosuppression	4 mg/kg PO q24h	unknown			
Meloxicam (Metacam)	Analgesia, antiinflammatory	0.2 mg/kg PO once, then 0.1 mg/kg PO q24h	none			
Methotrexate (Rheumatrex)	Immunosuppression	2.5 mg/M² PO q48h	same			
Metronidazole (Flagyl)	Antibiotic	10-15 mg/kg PO q8h	same			
, 5		7.5 mg/kg IV q8h	same			
Pentosan polysulphate (Pentosan 100)	Chondroprotective	3 mg/kg lM q7d	none			
Piroxicam (Feldene)	Analgesia, antiinflammatory	0.3 mg/kg PO q48h	same			
Polysulfated glycosaminoglycans (Adequan)	Chondroprotective	3-5 mg/kg IM q4d for 8 tx, then q30d	same			
Prednisone	Immunosuppression	2-4 mg/kg PO q24h	2-6 mg/kg PO q24h			
Freditisofie	Antiinflammatory	0.5-1.0 mg/kg PO/24h	same			
Tramadol	Analgesia	2-5 mg/kg q12h	same			
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#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
FINE-NEEDLE ASPIRATION
IMPRESSION SMEARS
STAINING OF CYTOLOGIC SPECIMENS
INTERPRETATION OF CYTOLOGIC SPECIMENS

Normal Tissues Hyperplastic Processes Inflammatory Processes Malignant Cells Lymph Nodes

#### **GENERAL CONSIDERATIONS**

Evaluation of a cytologic specimen obtained by fine-needle aspiration (FNA) in small animals with suspected neoplastic lesions often yields information that can be used to make a definitive diagnosis, thereby circumventing the immediate need to perform a surgical biopsy. At our hospital, almost every mass or enlarged organ is evaluated cytologically before a surgical biopsy is performed because the risks and costs associated with FNA are considerably lower than those associated with surgical biopsy. Quite frequently, a definitive cytologic diagnosis allows for the clinician to institute a specific treatment (i.e., multicentric lymphoma treated with chemotherapy).

In a recent study of 269 cytologic specimens from dogs, cats, horses, and other animal species, the cytologic diagnosis completely agreed with the histopathologic diagnosis in approximately 40% of cases and partially agreed in 18% of the cases; complete agreement ranged from 33% to 66%, depending on the lesion and location, and was highest for skin/subcutaneous lesions and for neoplastic lesions (Cohen et al). Clinically applicable diagnostic cytologic techniques are summarized in this chapter, with emphasis on sample

collection and the cursory interpretation of the specimens. Although some clinicians are able to obtain sufficient diagnostic information, a board-certified veterinary clinical pathologist should always evaluate a cytologic specimen before any prognostic or therapeutic decisions are made.

#### FINE-NEEDLE ASPIRATION

In FNA a single cell suspension is obtained using a small-gauge needle (i.e., 23 to 25 gauge) of the appropriate length for the desired target organ or mass; this needle can be coupled to a 12- or 20-ml sterile, dry plastic syringe, but frequently this is not necessary. Tissues easily accessible using this technique include the skin and subcutis, deep and superficial lymph nodes, spleen, liver, kidneys, lungs, thyroid, prostate, and intracavitary masses of unknown origin (e.g., mediastinal mass).

If the clinician is aspirating superficial masses, sterile preparation of the site is not necessary. However, clipping and sterile surgical preparation should always be done when aspirating organs or masses within body cavities. Once the mass or organ has been identified by palpation or radiography, it should be manually isolated; manual isolation is not necessary when performing ultrasound-, computed tomography (CT)-, or fluoroscopy-guided FNAs. A needle, either by itself or coupled to a syringe, is then introduced into the mass or organ; if the "needle alone" technique is used, the needle is reinserted into the tissue/mass several times. If the needle-syringe technique is used, suction is applied to the syringe three or four times. If the size of the mass or lesion allows it, the needle is then redirected two or three times and the procedure is repeated. Before withdrawing the needle and syringe, the clinician should release the suction so as not to aspirate blood that would contaminate the sample or air that would make the sample irretrievable from the barrel of the syringe. The needle is then detached, air is aspirated into the syringe, the needle is recoupled, and the sample is expelled onto a glass slide. In most cases no material is seen

in the syringe, and the amount of cells present within the hub of the needle is usually adequate to obtain four to eight good-quality smears. When the clinician is using the "needle alone" technique, the mass or lesion is isolated as described, and the needle is inserted into the lesion four to six times. This allows the clinician to core out small samples, which will be completely contained within the hub of the needle. Once a sample has been obtained, a clean disposable syringe is loaded with air and coupled to the needle, and the specimen is then gently expelled onto slides.

An aspiration gun (or handle) facilitates the acquisition of specimens by FNA, particularly in hard-to-reach areas such as a solitary small mass in the abdominal cavity. A 12-or 20-ml AspirGun (The Everest Co., Linden, N.J.), which easily fits onto a Monoject syringe, can be used.

Superficial ulcerated masses can easily be sampled by scraping their surface with a sterile scalpel blade, wooden tongue depressor, or gauze. Smears are then made either by touching a glass slide onto the ulcerated lesion (see the following section on impression smears) or by further scraping the surface with a tongue depressor and transferring the material thus obtained onto the slide. "Pull" smears made using two glass slides are preferable over "push" smears. Once the smears have been made, they are air-dried and stained using any of the techniques described in the next section.

#### IMPRESSION SMEARS

Impression smears of surgical specimens or open lesions are commonly used in practice. At our clinic, we evaluate numerous intraoperative impression smears to determine the therapeutic course to follow in a given patient.

When making impression smears from surgical specimens, the clinician first gently blots the tissue onto a gauze pad or paper towel to remove any blood or debris, then gently grasps it with forceps from one end. Touch imprints are made on a glass slide by gently touching the slide with the tissue specimen. I usually make two or three rows of impressions along the slide and then stain it. It is advisable to submit a different tissue specimen for histopathologic evaluation.

#### STAINING OF CYTOLOGIC SPECIMENS

Several staining techniques are practical for in-office use, including rapid Romanowsky's (e.g., Diff-Quik; various manufacturers) and new methylene blue (NMB) stains. Most commercial laboratories use Romanowsky's stains, such as Wright's or Giemsa.

There are some differences between these staining techniques. Romanowsky's stains are slightly more time consuming, but they produce better cellular detail and offer worse contrast between nucleus and cytoplasm; moreover, the smears can be permanently archived. NMB, on the other hand, is a quick stain (it takes literally seconds to stain a

smear), but it is not permanent, which means that slides cannot be saved for consultation; moreover, cellular details are not as sharp as they are on Romanowsky-stained smears. In addition, because nuclear DNA and RNA stain extremely well with this technique, most cells appear to be malignant. I routinely use Diff-Quik to get both a quick appreciation of the quality of the sample and, possibly, to arrive at a tentative diagnosis. This frequently allows a tentative diagnosis to be made while the client is still in the office. The main difference between rapid hematologic stains (e.g., Diff-Quik) and Giemsa or Wright-Giemsa stains is that, in a variable proportion of canine and feline mast cell tumors, the former do not stain the granules. In addition, rapid hematologic stains do not stain granules in some large granular lymphocytes (LGLs) or in eosinophils from Greyhounds (and some Golden Retrievers).

## INTERPRETATION OF CYTOLOGIC SPECIMENS

Although the clinician should strive to evaluate cytologic specimens proficiently, the ultimate cytologic diagnosis should be made by a board-certified veterinary clinical pathologist. The following are guidelines for cytologic interpretation. As a general rule, cytologic specimens are classified into one of the following six categories: normal tissue, hyperplasia/dysplasia (difficult to diagnose), inflammation, neoplasia, cystic lesions (contains fluid of various types), or mixed cellular infiltrate. The latter is usually either a malignant tumor with ongoing inflammation (e.g., squamous cell carcinoma with neutrophilic inflammation) or a hyperplastic tissue secondary to chronic inflammation (e.g., chronic cystitis with epithelial hyperplasia/dysplasia). Cytology of cystic lesions will not be discussed in this chapter.

## **NORMAL TISSUES**Epithelial Tissues

Most epithelial cells, particularly those of the glandular or secretory epithelium, tend to cling together (i.e., they have desmosomes), forming clusters or sheets. Individual cells are easily identifiable and are round or polygonal; nuclei and cytoplasms are well differentiated. Most cells in Romanowsky-stained smears have blue cytoplasm and round nuclei.

#### Mesenchymal Tissues

Cells from mesenchymal tissues (e.g., fibroblasts, fibrocytes, chondroblasts) are difficult to obtain in routine FNA material or tissue scrapings because they are usually surrounded by intercellular matrix. Mesenchymal cells are typically spindle shaped, polygonal, or oval and have irregular nuclei; cytoplasmic boundaries are usually indistinct, and cell clumps are seen rarely.

#### **Hematopoietic Tissues**

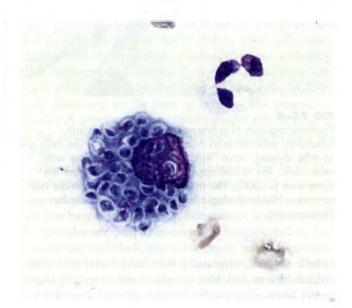
A detailed morphologic description of circulating blood cells is beyond the scope of this chapter. Briefly, however, most cells from hemolymphatic organs are round, individual cells (with no tendency to clump); they have a blue cytoplasm on Romanowsky-stained smears and a variable nuclear size; most nuclei are round or kidney shaped. Tissue such as bone marrow has cells in different stages of development (i.e., from blasts to well-differentiated circulating cells).

#### **HYPERPLASTIC PROCESSES**

Hyperplasia of different tissues commonly results in enlargement of glandular organs and lymphoid structures. The cytologic features of epithelial and lymphoid hyperplasia differ; lymphoid hyperplasia is discussed later in this chapter. Cytologically, hyperplastic changes may be difficult to recognize because they may mimic either normal or neoplastic tissues. Care should be taken when evaluating specimens from organs such as enlarged prostates or thickened urinary bladders because the high degree of hyperplasia and dysplasia frequently suggests malignancy.

#### **INFLAMMATORY PROCESSES**

Most inflammatory reactions are characterized cytologically by the presence of inflammatory cells and debris in the smear. The type of cell present depends on the etiologic agent (e.g., neutrophils in pyogenic infections, eosinophils in parasitic or allergic reactions) and the duration of the inflammatory process (i.e., acute processes are usually characterized by a predominance of granulocytes, whereas macrophages and lymphocytes predominate in chronic processes). The following pathogens are frequently identified in cytologic specimens: *Histoplasma*, *Blastomyces*, *Sporothrix*, *Cryptococcus*, *Coccidioides*, *Aspergillus/Penicillium*, *Toxoplasma*, *Leishmania*, other rickettsial agents (e.g., salmon poisoning), bacteria, and *Demodex* (Fig. 75-1).



Photomicrograph of a *Histoplasma capsulatum*–laden macrophage obtained from an ulcerated mucocutaneous lesion in a 6-year-old female, spayed black Labrador Retriever (×1000).

#### **MALIGNANT CELLS**

The cells that make up most normal organs and tissues (with the exception of bone marrow precursors) are well differentiated in that most of them are similar in size and shape, they have a normal nuclear: cytoplasmic (N:C) ratio, the nuclei usually have condensed chromatin and no nucleoli, and the cytoplasm may exhibit features of differentiation (e.g., keratin formation in squamous epithelium).

Malignant cells have one or more of the following features (Box 75-1): a high N: C ratio (i.e., larger nucleus and smaller cytoplasm); a delicate chromatin pattern; nucleoli (usually multiple); anisokaryosis (i.e., cells have nuclei of different sizes); nuclear molding (i.e., a nucleus in a multinucleated cell is compressed by a neighboring one); morphologic homogeneity (i.e., all cells look alike); pleomorphism (i.e., cells in different stages of development); vacuolization (primarily in malignant epithelial tumors); anisocytosis (i.e., cells are of different sizes); multinucleated giant cells; and, occasionally, phagocytic activity. Another feature of malignancy is heterotopia (i.e., the presence of a given cell type where it is not found anatomically); for example, epithelial cells can appear in a lymph node only as a consequence of metastasis from a carcinoma. In addition, malignant cells tend to be morphologically different from the progenitor cell population (see Box 75-1). On the basis of the predominant cytologic features, malignancies can be classified as carcinomas (epithelial), sarcomas (mesenchymal), or round (or discrete) cell tumors (Fig. 75-2).

#### Carcinomas

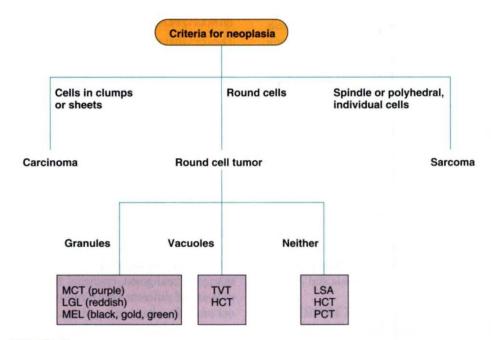
Most carcinomas are composed of round or polygonal cells that tend to cling together, forming clusters or large sheets. Their cytoplasms are usually deep blue, and in most adenocarcinomas vacuolization is evident. Cytoplasmic boundaries are difficult to recognize, and the cells resemble a mass of protoplasm rather than a sheet of individual cells. In squamous cell carcinomas cells are usually individualized, can be irregular or polygonal, have a deep blue cytoplasm (with an



BOX 75-1

Cytologic Characteristics of Malignant Neoplasms

Large nuclei
Fine chromatin pattern
One or more nucleoli
Anisokaryosis
Nuclear molding
Monomorphism
Pleomorphism
Anisocytosis
Cytoplasmic vacuolization
Cytoplasmic basophilia
Multinucleated giant cells
Phagocytosis
Heterotopia



Flow chart for the cytologic diagnosis of tumors in dogs and cats. MCT, Mast cell tumor; LGL, large granular lymphoma; MEL, melanoma; TVT, transmissible venereal tumor; HCT, histiocytoma; LSA, lymphoma; PCT, plasma cell tumor.

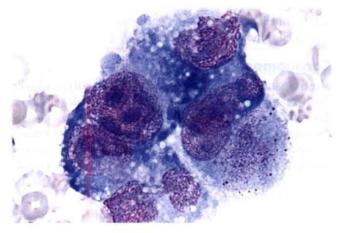


FIG 75-3

Photomicrograph of pleural fluid from an older female Irish Setter showing a cluster of deeply basophilic cells, with vacuolated cytoplasm, anisocytosis, anisokaryosis, and prominent nucleoli. The cytologic diagnosis was carcinomatosis (i.e., metastatic adenocarcinoma of unknown origin) (×1000).

occasional eosinophilic fringe), and have large vacuoles; neoplastic cells in squamous cell carcinomas frequently exhibit leukophagia. Nuclei in both adenocarcinomas and squamous cell carcinomas are large, with a fine chromatin pattern and evident nucleoli (Fig. 75-3).

#### Sarcomas

The cytologic features of sarcomas vary according to the histologic type. However, most mesenchymal tumors have

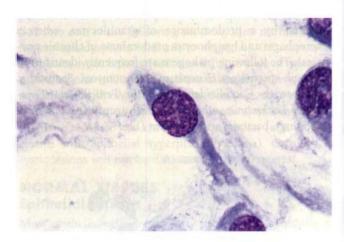


FIG 75-4

Photomicrograph of a fine-needle aspirate of a firm, lobulated, subcutaneous mass in an older dog. The cells are spindle shaped, have "tails," and do not associate with other cells. The nuclei appear to be protruding from the cytoplasm (×1000). The cytologic diagnosis is spindle cell sarcoma. Histopathologic findings were diagnostic for fibrosarcoma.

spindle shaped, polygonal, polyhedral, or oval cells, with a reddish blue to dark blue cytoplasm and irregularly shaped nuclei. Most cells are individualized, although clumping may occur (particularly in impression smears). The cells in most sarcomas have a tendency to form "tails," and the nuclei protrude from the cytoplasm (Fig. 75-4). The presence of spindle-shaped or polygonal cells with a vacuolated bluegray cytoplasm is highly suggestive of hemangiosarcoma.

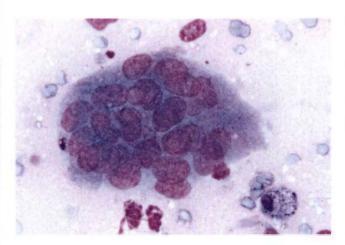


FIG 75-5
Photomicrograph of a multinucleated giant cell from a soft tissue sarcoma in a 13-year-old cat with tumor-associated hypercalcemia that resolved after surgical excision of the primary mass (×400).

Intercellular matrix (e.g., osteoid, chrondroid) is found occasionally; in these two tumor types the cells are usually round or ovoid. Multinucleated giant cells are common in some sarcomas in cats (Fig. 75-5).

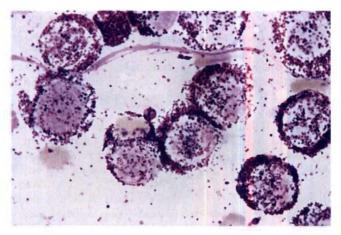
As a general rule, because sarcoma cells do not exfoliate easily, aspirates of these masses may yield false-negative results. Therefore, if a mass is clinically suspected to be a sarcoma and FNA findings are negative, a core biopsy specimen of the mass should be obtained.

#### **Round (Discrete) Cell Tumors**

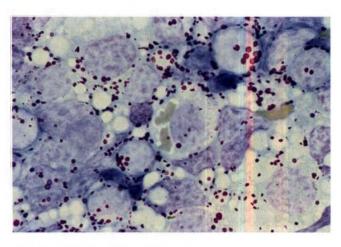
Tumors composed of a homogeneous population of round (or discrete) cells are referred to as *round* (or *discrete*) cell tumors (RCTs). These tumors are common in dogs and cats and include lymphoma, histiocytoma, mast cell tumor, transmissible venereal tumor, plasma cell tumor, and malignant melanoma; as discussed above, osteosarcomas and chondrosarcomas can be composed of round cells. RCTs are easily diagnosed on the basis of cytology; the presence or absence of cytoplasmic granules or vacuoles and the location of the nucleus aid in the classification of RCTs (see Fig. 75-2).

The cells that make up mast cell tumors (Fig. 75-6), LGL lymphomas (Fig. 75-7), and melanomas (Fig. 75-8) usually have cytoplasmic granules; cells in neuroendocrine tumors can also have granules. When hematologic stains are used, the granules are purple in mast cell tumors; red in LGL lymphomas; and black, green, brown, or yellow in melanomas. Lymphomas (Fig. 75-9), histiocytomas (Fig. 75-10), plasma cell tumors, and transmissible venereal tumors do not have cytoplasmic granules. Cells in osteosarcomas occasionally have small to large pink cytoplasmic granules (osteoid). Cytoplasmic vacuoles are common in transmissible venereal tumors and in histiocytomas.

Briefly, large cell lymphomas are characterized by a monomorphic population of individual undifferentiated

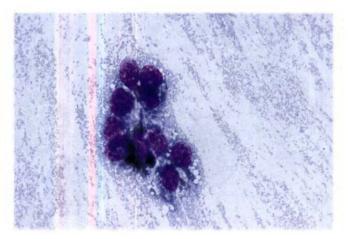


Photomicrograph of a fine-needle aspirate from a subcutaneous mass in an older Boxer with multiple dermoepidermal and subcutaneous masses and marked multifocal lymphadenopathy. Note the monomorphic population of round cells containing purple granules. The cytologic diagnosis was mast cell tumor (×1000).



Photomicrograph of an impression smear from a mesenteric lymph node in an old cat evaluated because of vomiting and diarrhea. Note the large round cells with red, large cytoplasmic granules. The diagnosis was lymphoma of large granular lymphocytes (×1000).

round cells with large nuclei, a coarse chromatin pattern, and one or two nucleoli; occasional cells may be vacuolated (see Fig. 75-9). Small and intermediate cell lymphomas may be difficult to recognize cytologically because the neoplastic population may resemble normal lymphocytes. Cells in histiocytomas are similar to those in lymphomas except that the chromatin pattern is fine rather than coarse, they have more abundant cytoplasm, and they are frequently vacuolated (see Fig. 75-10). Because inflammation is an important component of histiocytomas, inflammatory cells (i.e., neutrophils, lymphocytes) are commonly found in these tumors. Mast cell tumors are distinctive in that the cytoplasm of the cells



Photomicrograph of a fine-needle aspirate from a mass in the oral cavity of a 10-year-old Schnauzer. Note the dark, fine granules in the cytoplasm. The diagnosis was melanoma (×400).

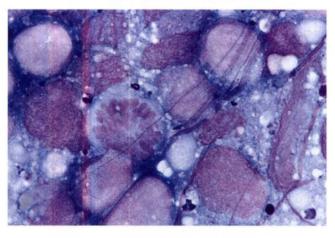


FIG 75-9

Photomicrograph of a fine-needle aspirate from the kidney of a middle-aged Boxer with bilateral renomegaly. Note the monomorphic population of round cells, with large nuclei, prominent nucleoli, and no cytoplasmic granules or vacuoles. A mitotic figure is seen in the center. The cytologic diagnosis was lymphoma (×1000).

contains purple (metachromatic) granules, which can be so numerous as to obscure the nuclear features; eosinophils are also a common feature in these tumors. Mast cell granules may be absent in poorly differentiated tumors or in tumors stained with Diff-Quik.

#### LYMPH NODES

Cytologic evaluation of lymph node aspirates is commonly done in practice. At our clinic, a cytologically based diagnosis is obtained in approximately 90% of dogs and 60% to 75% of cats with lymphadenopathy. If the cytologic findings of an enlarged lymph node are inconclusive, the node should be surgically excised and submitted for histopathologic evaluation.

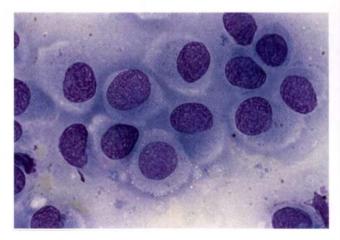


FIG 75-10

Photomicrograph of a fine-needle aspirate from a small, round, dermoepidermal mass in the head of a 1-year-old dog. Note the large round cells with abundant clear cytoplasm and fine chromatin pattern. The diagnosis was histiocytoma (×1000).

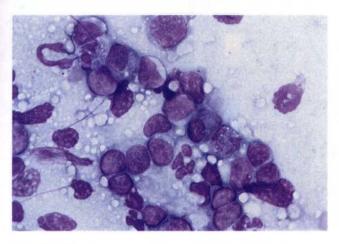
When evaluating cytologic specimens prepared from lymph node aspirates or impression smears, the clinician should keep in mind that these organs react to a variety of stimuli following a distinct pattern. In general, four cytologic patterns are recognized: normal lymph node, reactive or hyperplastic lymphadenopathy, lymphadenitis, and neoplasia.

#### **Normal Lymph Node**

Cytologic specimens from normal nodes are composed predominantly (75% to 90%) of small lymphocytes. These cells are approximately 7 to 10 µm in diameter (1 to 1.5 times the diameter of a red blood cell) and have a dense chromatin pattern and no nucleoli. The remaining cells are macrophages, lymphoblasts, plasma cells, and other immune cells.

## Reactive or Hyperplastic Lymphadenopathy

Lymphoid tissues reacting to different antigenic stimuli (e.g., bacterial, immunologic, neoplastic, fungal) are cytologically similar in that the cell population is composed of a mixture of small, intermediate, and large lymphocytes; lymphoblasts; plasma cells; and macrophages (Fig. 75-11). In addition, other cell types may be present, depending on the specific agent (e.g., eosinophils in parasitic or allergic reactions). The first impression when evaluating a reactive or hyperplastic node cytologically is that of a heterogeneous population of cells. The presence of cells in different stages of development indicates that the lymphoid tissue is undergoing polyclonal expansion (i.e., response to multiple antigens). Reactive lymph nodes in cats frequently lack plasma cells but contain large numbers of lymphoblasts, so they may be difficult to distinguish from lymphoma.



#### FIG 75-11

Photomicrograph of a fine-needle aspirate from a reactive lymph node in a dog. Note the heterogeneous population of lymphoid cells (small, medium, and large), plasma cells, and macrophages (×1000).

#### Lymphadenitis

Inflammatory processes affecting the lymph nodes produce cytologic changes similar to the ones seen in reactive lymphadenopathy, although there is a profusion of inflammatory cells (e.g., neutrophils in suppurative infections) and degenerative changes (e.g., pyknosis, karyorrhexis) in most cell lines. The etiologic agents may be visualized.

#### Neoplasia

Neoplastic cells can appear in a lymph node either as a result of lymphatic or vascular dissemination (i.e., metastasis from a primary tumor distal to the node) or as a primary process affecting these structures (i.e., lymphomas). Cytologic features of metastatic lymph node lesions consist of a reactive pattern and the presence of neoplastic cells; in advanced metastatic lesions it is frequently difficult to identify normal lymphoid cells. The morphology of the metastatic cells depends on the primary tumor type. As discussed in the preceding section, lymphomas are characterized by a monomorphous population of large, immature lymphoid cells; these cells are usually large and have an abnormally low N:C ratio, coarse chromatin, and evident nucleoli (see Fig. 75-9). As discussed previously, small cell lymphomas are difficult to diagnose cytologically.

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### CHAPTER

# Principles of Cancer Treatment



#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
PATIENT-RELATED FACTORS
OWNER-RELATED FACTORS
TREATMENT-RELATED FACTORS

#### **GENERAL CONSIDERATIONS**

Over the past several decades, a variety of therapeutic modalities have been used in dogs and cats with cancer (Box 76-1). However, until two or three decades ago, surgery remained the mainstay of cancer treatment for pets. Today, nonresectable or metastatic malignancies can be treated with varied degrees of success, using some of the modalities listed in Box 76-1.

When evaluating a cat or a dog with malignancy, the clinician should bear in mind that in most cases owners elect to treat their pets, if given the option. Although euthanasia still remains a reasonable choice in some small animals with cancer, every effort should be made to investigate treatment options.

Depending on the tumor type, biologic behavior, and clinical stage, a clinician may recommend one or more of the treatments listed in Box 76-1. However, in addition to tumor-related factors, many other factors influence the selection of the optimal treatment for a pet with cancer. These include patient-related, owner-related, and treatment-related factors.

#### PATIENT-RELATED FACTORS

It is important to remember that the best treatment for a particular tumor does not necessarily constitute the best treatment for a particular patient or the best treatment from the owner's perspective. The most important patient-related factor to be considered is the animal's general health and activity or performance status (Table 76-1). For example, a

cat or dog with markedly diminished activity and severe constitutional signs (i.e., poor performance status) may not be a good candidate for aggressive chemotherapy or the repeated anesthetic episodes required for external beam radiotherapy. Age by itself is not a factor that should be considered when discussing cancer therapy with the owner (i.e., "age is not a disease"). For example, a 14-year-old dog in excellent health is a better candidate for chemotherapy or radiotherapy than a 9-year-old dog with chronic kidney disease or decompensated congestive heart failure. Patient-related factors should be addressed before instituting specific cancer treatment (e.g., correct the azotemia, improve the nutritional status with enteral feeding).

#### OWNER-RELATED FACTORS

Owner-related factors play an important role in determining the treatment to be implemented in small animals with cancer. Every clinician is aware of the impact of the ownerpet bond. This bond is so important that it often dictates the treatment approach used in a given patient. For example, owners may be so apprehensive about having their dog with lymphoma receive chemotherapy that they refuse such treatment; thus the optimal treatment cannot be used in this patient.

In my experience, pet owners should be made a part of the medical team. If they are assigned tasks to perform at home, such as measuring the tumors to monitor the response to treatment, taking their pet's temperature daily, and monitoring their pet's performance status, they assume responsibility for the fate of their pet and are therefore quite cooperative. The clinician should always be available to answer concerned pet owners' questions and guide them through difficult times. The clinician should discuss all potential treatment options with the owner, emphasizing the pros and cons of each (e.g., beneficial effects and potential for adverse effects of treatment A versus B versus C versus no treatment). The clinician should also clearly explain what will (or should) happen during the pet's treatment, including a thorough description of the potential adverse effects by



#### Treatment Options for Animals with Cancer

Surgery Radiotherapy Chemotherapy Targeted molecular therapy Immunotherapy (biologic response modifiers) Hyperthermia Cryotherapy Phototherapy Photochemotherapy Thermochemotherapy Unconventional (alternative)



TABLE 76-1

Modified Karnovsky's Performance Scheme for Dogs and Cats

GRADE	ACTIVITY/PERFORMANCE					
0-Normal	Fully active, able to perform at predisease level					
1 — Restricted	Restricted activity from predisease level but able to function as an acceptable pet					
2—Compromised	Severely restricted activity level; ambulatory only to the point of eating but consistently defecating and urinating in acceptable areas					
3—Disabled	Completely disabled; must be force- fed; unable to confine urinations and defecations to acceptable areas					
4-Dead						

Modified from International Histological Classification of Tumors of Domestic Animals, Bull World Health Organ 53:145, 1976.

presenting different case scenarios (i.e., best-case scenario versus worst-case scenario). By observing these easy steps, the clinician usually cultivates realistic expectations on the part of the owner and ensures that the interaction with the owner is smooth and uneventful. As discussed in later paragraphs, the option of euthanasia may also be addressed at this time, either as an immediate option or as an eventual option if treatments fail.

Another very important owner-related factor is finances. In general, the treatment of a cat or dog with disseminated or metastatic malignancy is relatively expensive, as judged by the average clinician. However, it is the owner who should determine whether this treatment is indeed too costly. It is relatively common for an owner to spend \$3,000 to \$10,000 to treat a dog or cat with surgery, radiotherapy, or chemotherapy. In other words, all treatment options should be described and offered to the pet owner, regardless of their cost. Occasionally, owners spend what most people consider to be exorbitant amounts of money to treat their pet with cancer or other diseases.

#### TREATMENT-RELATED FACTORS

Several important treatment-related factors must be considered when planning cancer therapy. First, the specific indication should be considered. Surgery, radiotherapy, and hyperthermia are treatments aimed at eradicating a locally invasive tumor with a low metastatic potential (and potentially curing the patient), although they can be used palliatively in dogs or cats with extensive (bulky) disease or in those with metastatic disease. On the other hand, chemotherapy usually does not constitute a curative treatment, although palliation of advanced disease can easily be accomplished for several tumor types. Immunotherapy (the use of biologic response modifiers) also constitutes an adjuvant or palliative approach (i.e., tumors are not cured by immunotherapy alone). Recently, targeted molecular therapy aims at blocking specific pathways present in neoplastic but not in normal cells. In general, it is best to use an aggressive treatment when the tumor is first detected (because this is when the chances of eradicating every single tumor cell are the highest) rather than to wait until the tumor is in an advanced stage—that is, to "treat big when the disease is small." Removing "only" 99% of the tumor cells will not lead to a cure.

In some cases, the highest success rates are obtained by combining two or more treatment modalities. For example, the combination of surgery and chemotherapy (with or without immunotherapy) has resulted in a significant prolongation of disease-free survival in dogs with osteosarcoma of the appendicular skeleton and in dogs with splenic hemangiosarcoma. Similarly, the combination of surgery and radiotherapy has resulted in a prolongation of disease-free survival in dogs and cats with spindle cell sarcomas.

The complications and adverse effects of different treatments also constitute treatment-related factors to be considered when planning therapy. Complications of chemotherapy are addressed in Chapter 78. As discussed later, the animal's quality of life should be maintained (or improved) during cancer treatment. At our clinic, this is the priority in a cat or a dog with cancer receiving treatment. Our motto is "The patient should feel better with the treatment than with the disease."

Cancer treatment can be either palliative or curative. Given the current paucity of information regarding specific tumor types and treatments, these two approaches sometimes overlap (i.e., a treatment initially thought to be palliative may result in cure, or vice versa). As discussed earlier, every effort should be made to eradicate every single cancer cell in the body (i.e., obtain a cure) shortly after diagnosis. This means taking immediate action rather than adopting a wait-and-see attitude. With very few exceptions, malignancies do not regress spontaneously. In other words, by delaying treatment in an animal with confirmed malignancy, the



BOX 76-2

#### Criteria Used to Assess Tumor Response to Treatment

Complete remission (CR): complete disappearance of all tumors

Partial remission (PR): decrease in the bidimensional tumor diameter by more than 50%

Stable disease (SD): less than 25% variation in bidimensional tumor diameter

Progressive disease (PD): increase in the bidimensional tumor diameter by more than 25%

clinician is only increasing the probability that the tumor will disseminate locally or systemically, thereby decreasing the likelihood of a cure. As discussed earlier, surgery and radiotherapy are potentially curative treatments, whereas chemotherapy and immunotherapy are usually palliative.

If a cure cannot be obtained, the two main goals of treatment are to induce remission while achieving a good quality of life. The term remission refers to shrinkage of the tumor. When objectively evaluating the effects of therapy, the clinician should measure the tumor or tumors and assess the response using the criteria given in Box 76-2. The qualityof-life issue is quite important in small animal oncology (see preceding paragraphs). In a quality-of-life survey of owners whose pets had undergone chemotherapy for nonresectable or metastatic malignancy conducted in our clinic, more than 80% responded that the quality of life of their pets was maintained or improved during treatment. If a good quality of life cannot be maintained (i.e., the animal's performance status deteriorates), the treatment being used should be modified or discontinued. We are currently conducting a prospective study evaluating quality of life and pain before, during, and after therapy in dogs and cats with cancer.

Palliative treatments are quite acceptable for small animals with cancer and to their owners. For example, even though chemotherapy rarely achieves a cure for most tumors, veterinarians can provide a cat or dog (and its owner) with a prolonged, good-quality survival. Although these patients ultimately die of tumor-related causes, the owners are usually pleased to have a pet that is asymptomatic for a long time. Another common example that is frequently forgotten is palliative surgery; for example, in dogs or cats with ulcerated mammary carcinomas and small pulmonary metastases, euthanasia was once recommended. However, it is now known that performing a mastectomy or lumpectomy (even if the owners decline chemotherapy) is likely to result in several months of good-quality survival, until the metastatic

lesions finally cause respiratory compromise. In another example, dogs with apocrine gland adenocarcinoma of the anal sacs and metastatic sublumbar lymphadenopathy benefit from surgical resection of the primary tumor and/or metastatic nodes, even if adjuvant chemotherapy will not be considered. Removal of the primary mass improves clinical signs of straining in these patients; because the colon and rectum are compressed ventrally by the enlarged lymph nodes and laterally or dorsally by the primary mass, removal of one of the lesions easily alleviates clinical signs. Sublumbar (or iliac) lymphadenectomy and chemotherapy in dogs with metastatic apocrine gland adenocarcinoma of the anal sacs in our clinic result in survival times of 1 to 3 years.

Needless to say, the clinician should also address the presence of paraneoplastic syndromes even if specific antineoplastic therapy is not contemplated. For example, treatment of hypercalcemia of malignancy with bisphosphonates causes remarkable improvement in the quality of life of affected dogs. We have used either etidronate (Didronel, Procter and Gamble Pharmaceuticals, Cincinnati, Ohio, at a dosage of 10 to 20 mg/kg, administered orally q12h) or pamidronate (Aredia, Novartis Pharmaceuticals, East Hannover, N.J., at a dosage of 1 to 2 mg/kg, administered intravenously q6-8 weeks) in dogs with tumor-associated hypercalcemia in which the neoplastic disease could not be surgically removed or that had failed chemotherapy. In most dogs serum calcium concentrations were maintained within normal limits, and no appreciable toxicity was detected.

Finally, most cats and dogs with cancer are treated using a team approach. This team includes the pet, the owner, the medical oncologist, the oncologic nurse, the surgical oncologist, the radiotherapist, the clinical pathologist, and the pathologist. A smooth interaction among the members of the team results in marked benefits for the pet and its owner.

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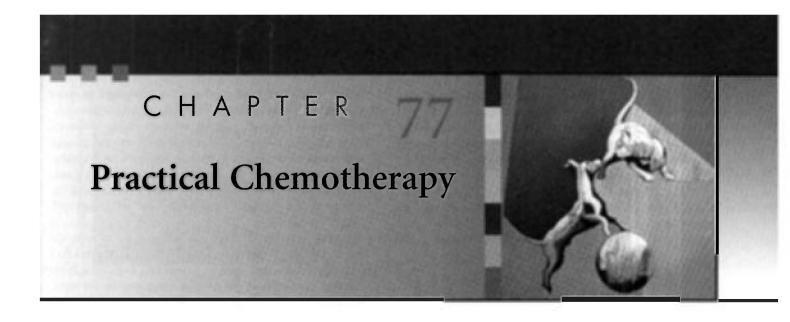
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#### CHAPTER OUTLINE

CELL AND TUMOR KINETICS
BASIC PRINCIPLES OF CHEMOTHERAPY
INDICATIONS AND CONTRAINDICATIONS OF
CHEMOTHERAPY
MECHANISM OF ACTION OF ANTICANCER DRUGS
TYPES OF ANTICANCER DRUGS
SAFE HANDLING OF ANTICANCER DRUGS

#### **CELL AND TUMOR KINETICS**

To better understand the effects of chemotherapy on both neoplastic and normal tissues, it is necessary to have a basic understanding of cell biology and tumor kinetics. As a general rule, the biologic characteristics of neoplastic cells are similar to those of their normal counterparts, with the main difference being that neoplastic cells usually do not undergo terminal differentiation. Therefore the cell cycles of normal and neoplastic cells are similar.

The mammalian cell cycle has two apparent phases: mitosis and the resting phase. The resting phase is actually composed of four phases (Fig. 77-1):

- 1. Synthesis phase (S): DNA is synthesized.
- Gap 1 phase (G1): RNA and the enzymes needed for DNA production are synthesized.
- 3. Gap 2 phase (G2): The mitotic spindle apparatus forms
- 4. Gap 0 phase (G0): This is the true resting phase.

The mitosis phase is termed the *M phase*.

Oncogenes serve as checkpoints between different phases of the cell cycle.

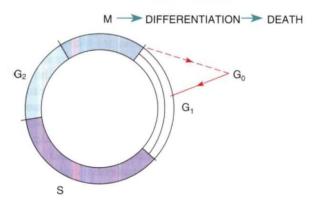
Several terms must be defined before chemotherapy is discussed. The *mitotic index* (*MI*) refers to the proportion of cells in the process of mitosis within a tumor; the pathologist often provides information about the mitotic activity in a given tumor sample, reported as the MI or as the number of

mitoses per high-power field (or per X number of highpower fields). The growth fraction (GF) refers to the proportion of proliferating cells within a tumor and cannot be quantified in a patient. The doubling time (DT) refers to the time it takes for a tumor to double in size; it can be calculated by using sequential measurements of the tumor volume  $[V = 1/6 \times (mean diameter)^3]$  seen on radiographs or ultrasonograms or determined by direct palpation. In dogs the DT ranges from 2 days (for metastatic osteosarcoma) to 24 days (for metastatic melanoma), whereas in humans it ranges from 29 days (for malignant lymphomas) to 83 days (for metastases from breast cancer). We recently evaluated the DT of pulmonary metastases in dogs with appendicular osteosarcoma treated with amputation and adjuvant chemotherapy; the median DT of the metastases was 13 days for Greyhounds and 21 days for nonGreyhounds. The DT depends on the time spent in mitosis, the cell cycle duration, the GF, and the cell loss resulting from death or metastasis. Given our knowledge of tumor kinetics, by the time a pulmonary metastatic nodule is visualized on radiographs, it consists of 200,000,000 cells, weighs less than 150 mg, and has already divided 25 to 35 times. A 1-cm palpable nodule has 109 tumor cells (1,000,000,000) and weighs 1 g (Fig. 77-2). As a general rule, most nonneoplastic tissues (with the exception of bone marrow stem cells and intestinal crypt epithelium) have a low GF, low MI, and prolonged DT, whereas most neoplastic tissues have a high MI, high GF, and short DT (at least initially; see Fig. 77-2).

Surgical cytoreduction (debulking) of a tumor that has reached a plateau of growth decreases the total number of cells, thus increasing the MI and GF and shortening the DT through yet unknown mechanisms (Fig. 77-3). In theory, this renders the neoplasm more susceptible to chemotherapy or radiotherapy.

#### **BASIC PRINCIPLES OF CHEMOTHERAPY**

Chemotherapeutic agents predominantly kill cells in rapidly dividing tissues. To exploit the tumoricidal effect of different chemotherapeutic drugs, it is common practice to combine three or more drugs to treat a given malignancy. These drugs are selected on the basis of the following principles: Each should be active against the given tumor type, each should act by a different mechanism of action, and they should not have superimposed toxicities. It is customary to name the protocol after the first letters of each drug in the combination (e.g., VAC for vincristine, doxorubicin [or Adriamycin], and cyclophosphamide). As a general rule, combination chemotherapy results in more sustained remissions and prolonged survival times, as compared with those achieved



Mammalian cell cycle. Cells in mitosis (M) can differentiate and subsequently die (the rule in normal tissues); they can also progress to  $G_0$  (true resting phase), from which they can be recruited by a variety of stimuli (see text).  $G_1$ ,  $G_2$ ,  $G_3$ ,  $G_4$ ,  $G_5$ ,  $G_7$ ,  $G_9$ 

using single-agent chemotherapy; this is thought to result from the fact that multichemotherapy delays (or even prevents) the development of drug-resistant clones. However, some exceptions to this rule include the treatment of dogs with osteosarcoma using cisplatin, carboplatin, or doxorubicin as single agents; the treatment of dogs with chronic lymphocytic leukemia using chlorambucil alone; and the treatment of dogs with transmissible venereal tumors with vincristine alone.

Another general concept of chemotherapy from the standpoint of cell kinetics is that it is more effective in a relatively small tumor than in a large one, even though the inherent sensitivity to the drug or drugs may be the same. As can be seen in Fig. 77-3, a small tumor (e.g., 10<sup>6</sup> cells) is more likely than a larger one (e.g., 10<sup>11</sup> cells) to be completely eradicated by the drugs because the smaller mass has a higher MI, a higher GF, and consequently a shorter DT than the larger mass (i.e., more cells are actively dividing at a given time).

Despite continued controversy, the doses of most chemotherapeutic agents are still determined on a body surface area (BSA) basis; exceptions will be listed later. This appears to provide a more constant metabolic parameter for comparing doses across species. It can be calculated using the following formula:

$$\frac{\text{Weight } (g)^{2/3} \times \text{K (constant)}}{10^4} = \text{m}^2 \text{ BSA}$$

The constant is 10.1 for the dog and 10 for the cat. Table 77-1 is a conversion table of weight (in kilograms) to BSA

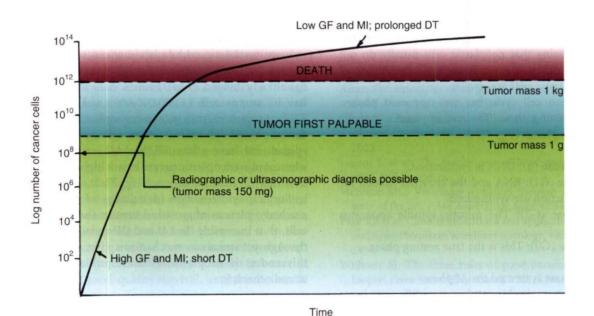


FIG 77-2
Tumor (cell) kinetics. Additional information on tumor kinetics can be found in the text. GF, Growth fraction; MI, mitotic index; DT, doubling time. (From Couto CG: Principles of chemotherapy. In Proceedings of the Tenth Annual Kal Kan Symposium for the Treatment of Small Animal Diseases: Oncology, Kalkan Foods, Inc, Vernon, Calif, 1986, p. 37.)

#### FIG 77-3

The effect of surgical or radiotherapeutic intervention on tumor kinetics. After cytoreduction, cells are recruited from the G<sub>0</sub> phase and the tumor returns to the exponential phase. XRT, Radiation therapy; GF, growth factor; MI, mitotic index; DT, doubling time. (From Couto CG: Principles of chemotherapy. In Proceedings of the Tenth Annual Kal Kan Symposium for the Treatment of Small Animal Diseases: Oncology, Kalkan Foods, Inc, Vernon, Calif, 1986, p. 37.)

Time

(in squared meters) for dogs. Table 77-2 is a conversion table of pounds (and kilograms) to BSA for cats. When drugs such as doxorubicin are being used, doses determined on the basis of BSA usually lead to adverse effects in very small dogs (i.e., those under 10 kg) and cats. A dose determined on the basis of weight (e.g., 1 mg/kg) is more appropriate in such small animals.

## INDICATIONS AND CONTRAINDICATIONS OF CHEMOTHERAPY

Chemotherapy is primarily indicated for animals with systemic (e.g., lymphoma, leukemias) or metastatic neoplasms, although it can also be used for the management of nonresectable, chemoresponsive neoplasms that have historically proved refractory to radiotherapy or hyperthermia (primary chemotherapy). It can also be used as an adjuvant treatment after partial surgical debulking of a neoplasm (e.g., partial excision of an undifferentiated sarcoma) and is indicated for the control of micrometastatic disease after the surgical excision of a primary neoplasm (e.g., cisplatin, carboplatin, or doxorubicin therapy after limb amputation in dogs with osteosarcoma; VAC after splenectomy for dogs with hemangiosarcoma). Chemotherapy can also be administered intracavitarily in dogs and cats with malignant effusions or neoplastic involvement of the cavity/area in question (e.g., intrapleurally administered cisplatin or 5-fluoruracil in dogs with pleural carcinomatosis). Finally, neoadjuvant, or primary, chemotherapy is the approach used in animals with bulky tumors not amenable to surgical excision. After the drugs cause the tumor to shrink, the tumor can be surgically



#### TABLE 77-1

Conversion of Body Weight to Body Surface Area in Dogs

	ight to Body Surface Area in Dogs
BODY WEIGHT (kg)	BODY SURFACE AREA (m²)
00.5	0.06
01	0.10
02	0.15
03	0.20
04	0.25
05	0.29
06	0.33
07	0.36
08 09	0.40
10	0.43 0.46
11	0.49
12	0.52
13	0.55
14	0.58
15	0.60
16	0.63
17	0.66
18	0.69
19	0.71
20	0.74
21 22	0.76 0.78
23	0.78
24	0.83
25	0.85
26	0.88
27	0.90
28	0.92
29	0.94
30	0.96
31	0.99
32	1.01
33 34	1.03
35	1.05 1.07
36	1.09
37	1.11
38	1.13
39	1.15
40	1.17
41	1.19
42	1.21
43	1.23
44	1.25
45	1.26
46	1.28
47	1.30
48 49	1.32
50	1.34 1.36
30	1.30



TABLE 77-2

Conversion of Body Weight to Body Surface Area in Cats

	, 8						
BODY WEIGHT	BODY WEIGHT (kg)	BODY SURFACE AREA (m²)					
5	2.3	0.165					
6	2.8	0.18 <i>7</i>					
7	3.2	0.207					
8	3.6	0.222					
9	4.1	0.244					
10	4.6	0.261					
11	5.1	0.278					
12	5.5	0.294					
13	6.0	0.311					
14	6.4	0.326					
15	6.9	0.342					
16	7.4	0.356					
1 <i>7</i>	<i>7</i> .8	0.371					
18	8.2	0.385					
19	8. <i>7</i>	0.399					
20	9.2	0.413					

excised; chemotherapy is then continued to eliminate any residual neoplastic cells (e.g., VAC chemotherapy for dogs with subcutaneous hemangiosarcomas).

As a general rule, chemotherapy should not be used as a substitute for surgery, radiotherapy, or hyperthermia; nor should it be used in animals with severe underlying multiple-organ dysfunction (or it should be used cautiously, with a dose modification) because this increases the risk of systemic toxicity.

## MECHANISM OF ACTION OF ANTICANCER DRUGS

The effects of anticancer drugs on a neoplastic cell population follow first-order kinetic principles (i.e., the number of cells killed by a drug or drug combination is directly proportional to one variable: the dose used). These drugs kill a constant proportion of cells, rather than a constant number of cells. Therefore the efficacy of a drug or drug combination depends on the number of cells in a given tumor (e.g., a drug combination that kills 99% of the cells in a tumor containing 100,000,000 [10<sup>9</sup>] cells leaves 1,000,000 [10<sup>6</sup>] viable cells).

As discussed in the following paragraphs, different types of anticancer drugs kill tumor cells by different mechanisms. Drugs that kill only dividing tumor cells (i.e., that do not kill cells in the G<sub>0</sub> phase) by acting on several phases of the cycle are termed *cell cycle phase-nonspecific drugs*. Alkylating agents belong to this group. Drugs that selectively kill tumor cells during a given phase of the cell cycle are termed *cell cycle phase-specific drugs*. Most antimetabolites and plant alkaloids are phase-specific drugs. Finally, drugs that kill neo-



Types of Anticancer Drugs

#### **Alkylating Agents**

- Cyclophosphamide
- Chlorambucil
- Melphalan
- CCNU (lomustine)
- Carboplatin

#### **Antimetabolites**

- Cytosine arabinoside
- Methotrexate
- 5-Fluorouracil; SHOULD NOT BE USED IN CATS!
- Azathioprine

#### **Antitumor Antibiotics**

- Doxorubicin
- Bleomycin
- Actinomycin D
- Mitoxantrone

#### Plant Alkaloids

- Vincristine
- Vinblastine
- Vinorelbine
- Etoposide or VP-16

#### **Hormones**

• Prednisone

#### Miscellaneous Agents

- DTIC
- L-Asparaginase

plastic cells regardless of their cycle status (i.e., they kill both dividing and resting cells) are termed *cell cycle-nonspecific drugs*. These latter drugs are extremely myelosuppressive (e.g., nitrosoureas) and are infrequently used in veterinary medicine.

#### **TYPES OF ANTICANCER DRUGS**

Anticancer drugs are commonly classified into six categories (Box 77-1). Most of these drugs are currently available as generic products.

Alkylating agents cross-link DNA, thus preventing its duplication. Because they mimic the effects of radiotherapy, they are also referred to as *radiomimetics*. These drugs are active during several phases of the cell cycle (i.e., they are cell cycle phase-nonspecific) and are more active if given intermittently at high doses. The major toxicities of these drugs are myelosuppressive and gastrointestinal in nature. Alkylating agents commonly used in pets with cancer are listed in Box 77-1.

Antimetabolites exert their activity during the S phase of the cell cycle (cell cycle phase-specific) and are more active if given repeatedly at low doses or as continuous intravenous infusions. These drugs are structural analogs of naturally occurring metabolites (fake metabolites) that substitute for normal purines or pyrimidines. The major toxicities of these drugs are myelosuppressive and gastrointestinal. Box 77-1 lists the antimetabolites commonly used in small animals with cancer.

Antitumor antibiotics act by several mechanisms (i.e., cell cycle phase-nonspecific), the most important of which appears to be DNA damage produced by free radicals or by a topoisomerase-II-dependent mechanism. There are now several synthetic or semisynthetic antibiotics. The major toxicities of these drugs are myelosuppressive and gastrointestinal in nature; doxorubicin and actinomycin D are extremely caustic if given perivascularly, and the former has cumulative cardiotoxic effects. Antitumor antibiotics are listed in Box 77-1.

Plant alkaloids are derived from the periwinkle plant (Vinca rosea) and the May apple plant (Podophyllum peltatum). Vinca derivatives disrupt the mitotic spindle and are therefore cell cycle phase-specific (active during M phase), whereas Podophyllum derivatives cross-link DNA. The major toxicity is perivascular sloughing if the agent extravasates. Etoposide should not be administered intravenously because the vehicle (Tween 80) causes anaphylaxis. Box 77-1 lists commonly used plant alkaloids.

Hormones are commonly used for the treatment of hemolymphatic malignancies or endocrine-related tumors. Commonly used hormones are listed in Box 77-1.

With the exception of corticosteroids, hormones are not recommended as antineoplastics because they are associated with relevant adverse effects in animals.

Miscellaneous agents consist of drugs with a mechanism of action that is either unknown or differs from those of agents already described. Box 77-1 lists miscellaneous agents commonly used in small animals with cancer.

A novel approach to anticancer chemotherapy is to exploit the use of molecular targets. For example, c-KIT mutations are commonly identified in human with chronic myelogenous leukemia; imatinib (Gleevec, Novartis) selectively block this tyrosine kinase (TK) pathway and induces apoptosis of neoplastic (but not normal) cells. Mutations of c-KIT are also common in canine mast cell tumors, where small molecule TK inhibitors other than imatinib have been effective. A new TK inhibitor is now available for veterinary use (Palladia, Pfizer). In the dog imatinib appears to be hepatotoxic.

## SAFE HANDLING OF ANTICANCER DRUGS

Cytotoxic drugs have very narrow therapeutic indices, with toxic effects very often noted at the standard therapeutic dosages. Occupational exposure, as might occur in personnel who commonly administer these drugs, has been docu-

mented in the literature; adverse effects, including headache, nausea, liver disease, and reproductive abnormalities, have been associated with this exposure. As such, no safe exposure level has been identified, and all possible measures to limit personnel exposure to cytotoxic drugs must be taken during their preparation and administration.

Reconstitution of cytotoxic drugs for administration must be performed in a biosafety level II vertical laminar airflow hood. Although the cost for this equipment is not prohibitively expensive for a large equine hospital (~\$6,000-\$10,000), this cost is currently not justified by the frequency of use. A new closed system (PhaSeal<sup>TM</sup>, Carmel Pharma, Columbus, OH) is practical and relatively inexpensive and limits operator and environmental drug exposure to almost zero. If containment devices are not available, cytotoxic drugs can be reconstituted at a human hospital or pharmacy or at a nearby small animal clinic with a sufficiently large oncology caseload. Care should be taken to respect the storage half-life of reconstituted drugs, and they should be administered to the patient as soon as possible after reconstitution. Drugs should be delivered in a clearly labeled, sealed plastic bag, and any handling of the drugs should be performed while wearing the appropriate personal protective gear.

Personal protective gear has been shown to all but eliminate detectable occupational exposure to cytotoxic drugs in human oncology nurses when combined with safe, conservative handling practices. All personnel present during chemotherapy administration to animal patients, including veterinarians, technicians, and ward staff, must wear thick latex chemotherapy gloves or two pairs of regular latex examination gloves. The thickness of the gloves is more important than the composition for barrier protection. Ideally, personnel should also wear impermeable disposable gowns, eye protection, and particle-filtering face masks. All fluid lines should be primed before addition of cytotoxic drugs to reduce environmental contamination, and all potentially contaminated supplies, including gowns, gloves, fluid bags, lines, and so forth, should be disposed of in properly labeled biohazard bags or plastic sharps containers. Disposal of material potentially contaminated with cytotoxic drugs may be arranged through a local human hospital; alternatively, an EPA-approved disposal facility should be located. Materials used in the preparation and administration of chemotherapy should not be reused. Patient waste, including urine and feces, should be disposed of similarly 24 to 48 hours after chemotherapy administration, and personnel involved in the husbandry of these patients should wear the above-recommended personal protective gear when attending patients.

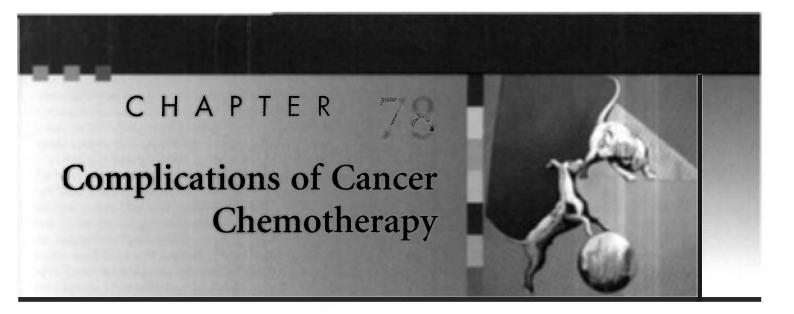
Protocols for handling spills should be prepared in advance and posted in areas where patients may be receiving chemotherapy. This area should be a designated area of the hospital with low traffic and minimal drafts; a stall may be selected for this purpose in equine hospitals. Isolation stalls will minimize exposure of personnel to chemotherapeutic agents. Once the patient has received chemotherapy, its cage should be clearly identified with a notice that contains

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information about precautions to be taken during handling of the animal and its wastes.

#### **Suggested Readings**

- Chabner BA et al: Cancer chemotherapy and biotherapy: principles and practice, ed 3, Philadelphia, 2001, Lippincott, Williams and Wilkins.
- Helfand SC: Principles and applications of chemotherapy, *Vet Clin N Am* 20:987, 1990.
- London CA et al. Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies, Clin Cancer Res 9:2755, 2003.
- Moore AS: Recent advances in chemotherapy for non-lymphoid malignant neoplasms, Compend Contin Educ Pract Vet 15:1039, 1993
- Vail DM: Recent advances in chemotherapy for lymphoma in dogs and cats, Compend Contin Educ Pract Vet 15:1031, 1993.



#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
HEMATOLOGIC TOXICITY
GASTROINTESTINAL TOXICITY
HYPERSENSITIVITY REACTIONS
DERMATOLOGIC TOXICITY
PANCREATITIS
CARDIOTOXICITY
UROTOXICITY
HEPATOTOXICITY
NEUROTOXICITY
PULMONARY TOXICITY
ACUTE TUMOR LYSIS SYNDROME

#### GENERAL CONSIDERATIONS

Because most anticancer agents are relatively nonselective, they kill not only rapidly dividing neoplastic tissues but also some of the rapidly dividing normal tissues in the host (e.g., villus epithelium, bone marrow cells). In addition, similar to other commonly used agents (e.g., digitalis glycosides), most anticancer agents have low therapeutic indices (i.e., narrow therapeutic:toxic ratios).

Because anticancer agents follow first-order kinetic principles (i.e., the fraction of cells killed is directly proportional to the dose used), increasing the dose of a particular drug increases the proportion of the neoplastic cells killed, but it also enhances its toxicity. This is commonly seen when a tumor relapses and higher doses of a previously prescribed chemotherapeutic agent are administered.

Because toxicity generally tends to affect rapidly dividing tissues, given the short doubling times of the bone marrow and villal epithelial cells, myelosuppression and gastrointestinal signs are the most common toxicities encountered in practice. Other rare complications of chemotherapy include anaphylactoid (or anaphylactic) reactions, dermatologic toxicity, pancreatitis, cardiotoxicity, pulmonary toxicity, neurotoxicity, hepatopathies, and urotoxicity. Table 78-1 lists

anticancer drugs commonly used in small animals and their toxicities.

Several factors can potentiate the effects of anticancer agents and thereby enhance their toxicity. For example, drugs that are excreted primarily through the kidneys (e.g., cisplatin, carboplatin, methotrexate) are more toxic to animals with renal disease; thus a dose reduction or the use of an alternative drug is usually recommended in such cases.

In addition to the direct effects of some drugs on different organ systems, rapid killing of certain neoplastic cells (i.e., lymphoma cells) can lead to sudden metabolic derangements that result in acute clinical signs mimicking those of drug toxicity (i.e., depression, vomiting, diarrhea). This syndrome is referred to as acute tumor lysis syndrome (ATLS) (see p. 1167).

In general, cats appear to be more susceptible than dogs to some of the adverse effects of chemotherapy (e.g., anorexia, vomiting) but not to others (e.g., myelosuppression). Certain breeds of dogs, including Collies and Collie crosses, Old English Sheepdogs, Cocker Spaniels, and West Highland White Terriers, also appear to be more prone to some of the acute adverse reactions to chemotherapy (i.e., gastrointestinal signs, myelosuppression) than the general dog population.

The overall prevalence of toxicity of different chemotherapy protocols is considerably lower in dogs and cats (approximately 5% to 40%) than in humans (75% to 100%) treated with similar drugs or combinations. A recent survey of owners whose pets had been treated with a variety of chemotherapy protocols at The Ohio State University Veterinary Teaching Hospital revealed that more than 80% considered their pets' quality of life to be equal to or better than that before the start of chemotherapy.

#### HEMATOLOGIC TOXICITY

The high mitotic rate and growth fraction (i.e., 40% to 60%) of the bone marrow cells predispose this organ to relevant toxicity from anticancer drugs. Hematologic toxicity constitutes the most common complication of chemotherapy, and



TABLE 78-1

#### Toxicity of Anticancer Agents in Cats and Dogs

TOXICITY	DOX	BLEO	ACT	СТХ	LEUK	CISP	MTX	araC	5-FU	L-ASP	VCR	VBL	DTIC	CCNU
Myelosuppression	S	Ν	М	M/S	N/M	М	M/S	M/S	Μ	N/M	N/M	M/S	M/S	M/S
Vomiting/diarrhea	M/S	Ν	Μ	M	N/M	M/S	M/S	N/M	N/M	Ν	N/M	N/M	M/S	M
Cardiotoxicity	M/S	Ν	Ν	Ν\ŝ	N	N	Ν	N	N	Ν	N	N	N	Ν
Neurotoxicity	N	Ν	Ν	N	Ν	Ν	Ν	Ν	M	N/Wš	N/M	Ν	Ν	Ν
Hypersensitivity	M/S	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	M/S	N	Ν	Ν	Ν
Pancreatitis	M	Ν	Ν	N/M	Ν	Ν	Ν	N/M	Ν	M/S	Ν	Ν	N/M	Ν
Perivascular sloughing	S	Ν	M/S	N	NA	N/M	Ν	N	N/M	N	M/S	M/S	M/S	Ν
Urotoxicity	Ś	Ν	N	M/S	Ν	M/S	M	Ν	N	Ν	N	N	N	M
Hepatotoxicity	Ν	N	N	N	Ν	N	Ν	Ν	Ν	Ν	Ν	Ν	Ν	M/S

DOX, Doxorubicin; BLEO, bleomycin; ACT, actinomycin D; CTX, cyclophosphamide; LEUK, chlorambucil; CISP, cisplatin; MTX, methotrexate; araC, cytosine arabinoside; 5-FU, 5-fluorouracil; L-asp, L-asparaginase; VCR, vincristine; VBL, vinblastine; DTIC, dacarbazine; CCNU, lomustine; S, severe; N, none; M, mild to moderate; NA, not applicable; ?, questionable.

often the severe and potentially life-threatening cytopenias that occur necessitate the temporary or permanent discontinuation of the offending agent or agents. Table 78-1 lists agents commonly implicated in this type of toxicity.

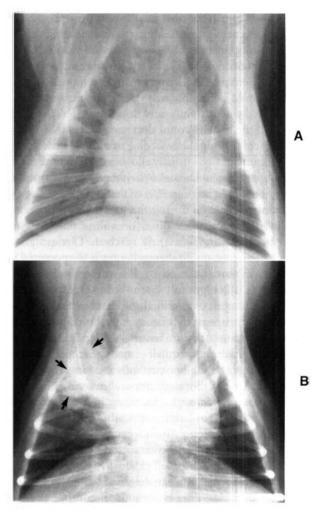
It is easy to anticipate the cell line that will be affected on the basis of the bone marrow transit times and circulating half-lives of blood-formed elements. For example, the bone marrow transit time and circulating half-life of red blood cells in the dog are approximately 7 and 120 days, those of the platelets are 3 days and 4 to 6 days, and those of granulocytes are 6 days and 4 to 8 hours, respectively. On the basis of this, neutropenia usually occurs first, followed by thrombocytopenia. Chemotherapy-induced anemia is rare in dogs and cats and, if it occurs, is of late onset (3 to 4 months after initiation of therapy). Other patient-related factors (e.g., malnutrition, old age, concurrent organ dysfunction, prior extensive chemotherapy) and tumor-related factors (e.g., bone marrow infiltration, widespread parenchymal organ metastases) can also affect the degree of myelosuppression.

Although thrombocytopenia is probably as common as neutropenia, it is rarely severe enough to cause spontaneous bleeding, and therefore it is not discussed at length here. In general, in most dogs with chemotherapy-induced thrombocytopenia, the platelet counts remain above 50,000 cells/µl. Spontaneous bleeding usually does not occur until platelet counts are below 30,000/µl. Some drugs and protocols are associated with predictable thrombocytopenia, including doxorubicin and dacarbazine (ADIC), D-MAC (see the table on cancer chemotherapy protocols at the end of Part 11), lomustine, and melphalan in dogs; platelet counts associated with these protocols are usually less than 50,000/µl. Chemotherapy-induced thrombocytopenia is extremely rare in cats. Thrombocytosis is common in cats and dogs receiving vincristine.

Neutropenia usually constitutes the dose-limiting cytopenia and occasionally leads to life-threatening sepsis in dogs; although neutropenia does occur in cats receiving chemotherapy, it rarely leads to the development of clinically recognizable sepsis. The nadir of neutropenia for most drugs (i.e., lowest point in the curve) usually occurs 5 to 7 days after treatment, and the neutrophil counts return to normal within 36 to 72 hours of the nadir. With certain drugs the nadir of neutropenia is delayed (i.e., approximately 3 weeks for carboplatin in dogs and cats). Dogs with neutrophil counts less than 2000 cells/ I should be closely monitored for the development of sepsis, although overwhelming sepsis rarely occurs in animals with neutrophil counts of more than 1000 cells/µl. The development of sepsis in neutropenic cats is extremely rare, or it goes unrecognized.

The pathogenesis of sepsis in neutropenic animals is as follows: First, the chemotherapy-induced death and desquamation of gastrointestinal crypt epithelial cells occur simultaneously with myelosuppression; next, enteric bacteria are absorbed through the damaged mucosal barrier into the systemic circulation (bacterial translocation); and, finally, because the number of neutrophils in the circulation is not sufficient to phagocytose and kill the invading organisms, multiple organs become colonized with the bacteria and death ensues, unless the animal is treated appropriately.

It is important to identify the septic neutropenic animal using laboratory means because the cardinal signs of inflammation (i.e., redness, swelling, increased temperature, pain, abnormal function) may be absent because there are not enough neutrophils to participate in the inflammatory process. The same holds true for radiographic changes compatible with inflammation; for example, dogs with neutropenia and bacterial pneumonia diagnosed on the basis of cytologic and microbiologic findings in transtracheal wash material often have normal thoracic radiographic findings (Fig. 78-1). As a general rule, if a severely neutropenic animal



Thoracic radiographs from a 5-year-old male, castrated Boston Terrier with multicentric lymphoma treated with doxorubicin and dacarbazine (ADIC) chemotherapy. This dog presented as an emergency because of depression, fever, and mild bilateral nasal discharge. The neutrophil count on admission was 1500/I. A, Thoracic radiograph findings were considered normal at the time, but a transtracheal wash specimen contained bacteria. B, Two days later, when the neutrophil count increased to 16,300/1, focal areas of pneumonia became evident. (From Couto CG: Management of complications of cancer chemotherapy, Vet Clin North Am 20:1037, 1990.)

(neutrophil count <500/ $\mu$ l) is evaluated because of pyrexia (>104° F [>40° C]), the fever should be attributed to bacterial pyrogens until proved otherwise and the patient should be treated aggressively with antimicrobial therapy (see following paragraphs). Neutropenic septic patients can also be hypothermic.

All dogs and cats undergoing chemotherapy should be up to date on their vaccines; it is controversial whether the use of modified-live vaccines should be avoided because of the potential for inducing illness in immunosuppressed animals. Recent evidence suggests that dogs with cancer undergoing chemotherapy have protective serum antibody titers for commonly used vaccines.

Hematologic monitoring of the patient receiving chemotherapy constitutes the most effective way to prevent (or anticipate) severe, life-threatening sepsis or bleeding secondary to myelosuppression. Complete blood counts (CBCs) should be obtained weekly or every other week (depending on the treatment protocol), and the myelosuppressive agent or agents should be temporarily discontinued (or the dose decreased) if the neutrophil count decreases to less than 2000 cells/µl or if the platelet count decreases to less than 50,000 cells/µl. Discontinuing the offending agent or agents for two or three administrations usually allows sufficient time for the cell counts to return to normal. When therapy is reinstituted, it is recommended that only 75% of the initial dose be given and the doses increased during the next 2 to 3 weeks until the initially recommended dose (or a dose that does not produce marked cytopenias) is reached. Obviously, the drawback of discontinuing chemotherapy is the potential for tumor relapse, so the clinician and owner must weigh the pros and cons of temporarily discontinuing treatment.

Clinically, neutropenic animals can be classified as febrile or afebrile. Neutropenic, febrile animals should be managed aggressively because they are usually septic. Thus fever in a neutropenic patient constitutes a medical emergency. The following protocol is the one currently used in such patients at our clinic. First, a thorough physical examination is performed to search for a septic focus, an indwelling intravenous (IV) catheter is placed aseptically, and IV fluids are administered as required. All anticancer agents are discontinued immediately, with the exception of corticosteroids, which should be discontinued gradually, if at all, because acute hypoadrenocorticism can develop in animals receiving steroid therapy if the drug is abruptly discontinued. Blood samples for a CBC and serum biochemical profile are obtained immediately. A urine sample for urinalysis and bacterial culture is also obtained, unless the patient is thrombocytopenic, in which case cystocentesis should be avoided to prevent intravesical bleeding. Two or three sets of aseptically collected blood samples can be obtained at 30-minute intervals for aerobic and anaerobic bacterial cultures and antibiotic susceptibility tests, although this is usually not necessary because the bacterial isolates are quite predictable (see following paragraph) and because the results of these tests will not be available for several days. After the second set of samples for blood cultures is collected, therapy with an

empirical bactericidal antibiotic combination is instituted. We use a combination of enrofloxacin (5 to 10 mg/kg IV q24h) and ampicillin (22 mg/kg IV q8h) because most bacterial isolates in such animals are Enterobacteriaceae and staphylococci, organisms commonly susceptible to these agents. Once the neutrophil count returns to normal and the animal's condition is clinically normal (usually within 72 to 96 hours), the antibiotic combination is discontinued and the animal is allowed to go home, with instructions to the owner to administer sulfadiazine-trimethoprim (ST) at a dosage of 13 to 15 mg/kg by mouth (PO) q12h or enrofloxacin (5 to 10 mg/kg PO q24h) for 5 to 7 days. When the patient returns for additional chemotherapy, the dose of the offending agent or agents should be decreased by 15% to 20%.

At our clinic the yield for three sets of blood cultures in dogs with cancer, fever, and normal-to-high neutrophil counts is approximately 40%, whereas it is approximately 30% in dogs with cancer, fever, and neutropenia. Isolates in the former group usually include *Streptococcus* spp., *Staphylococcus* spp., *Enterobacter* spp., *Klebsiella* spp., and *Escherichia coli*, in decreasing order of frequency. In neutropenic, febrile dogs the isolates include mainly *Klebsiella* spp. and *E. coli*; *Staphylococcus* spp. is isolated in fewer than 20% of the dogs.

Neutropenic, afebrile, asymptomatic patients can be treated as outpatients by discontinuing the drug or drugs as described earlier and administering ST (13 to 15 mg/kg PO q12h). The patient that is afebrile but has constitutional signs should be considered to be septic and treated as described in previous paragraphs. If the neutropenia is not severe (i.e., >2000 cells/µl), no therapy is required and the animal should only be observed by the owner. Owners should be instructed to take their pet's rectal temperature twice daily and to call the veterinarian if pyrexia develops, in which case the animal is treated as neutropenic and febrile. ST eliminates the aerobic intestinal florae but preserves the anacrobic bacteria, which are an important component of the local defense system because of their ability to produce local antibiotic factors. In addition, ST is active against many pathogens isolated from animals with cancer, and it achieves therapeutic blood and tissue concentrations and also high intragranulocytic concentrations.

Myelosuppression may be alleviated through the use of lithium carbonate (10 mg/kg PO q12h) in dogs or recombinant human granulocyte colony–stimulating factor (G-CSF; Neupogen; 5 µg/kg subcutaneously [SC] q24h) in dogs and cats. Although several studies have reported the beneficial role of G-CSF or granulocyte-macrophage colony–stimulating factor (GM-CSF) in dogs and cats, it is unlikely that these agents will find their way into the clinic owing to their high cost (approximately \$50 to \$150/day) and the fact that dogs and cats can mount an antibody response to this protein of human origin and inactivate it; moreover, in dogs with chemotherapy-induced neutropenia the activity of endogenous G-CSF is extremely high, and neutrophil counts return to normal within 36 to 72 hours, the same interval

reported for "response" to G-CSF. In our clinic G-CSF is typically reserved for patients that received accidental chemotherapy overdoses and in which the predicted duration of neutropenia is unknown.

#### GASTROINTESTINAL TOXICITY

Although less common than myelosuppression, gastrointestinal toxicity is a relatively common complication of cancer chemotherapy in pets. From a clinical standpoint, two major types of gastrointestinal complications can occur: gastroenterocolitis and the combination of anorexia, nausea, and vomiting.

Although results of controlled studies are not available, nausea and vomiting are not apparently as common in pets as they are in humans receiving similar drugs and dosages. Drugs associated with nausea and vomiting in dogs or cats include dacarbazine (DTIC), cisplatin, doxorubicin (primarily in cats), methotrexate, actinomycin D, cyclophosphamide, and 5-fluorouracil (5-FU; see Table 78-1).

Acute anorexia, nausea, and vomiting caused by injectable drugs are usually prevented by administering the offending agents by slow IV infusion. If these problems persist despite this tactic, antiemetics such as metoclopramide can be given at a dosage of 0.1 to 0.3 mg/kg IV, SC, or PO q8h, or prochlorperazinecan be administered intramuscularly at a dosage of 0.5 mg/kg q8-12h. Other antiemetics that may be effective in dogs with chemotherapy-induced emesis are butorphanol (Torbugesic; Fort Dodge Labs, Fort Dodge, Iowa) at a dosage of 0.1 to 0.4 mg/kg intramuscularly or intravenously every 6 to 8 hours and IV ondansetron (Zofran; Glaxo, Research Triangle Park, N.C.) at a dosage of 0.1 mg/kg immediately before chemotherapy and every 6 hours thereafter, or maropitant (Cerenia, Pfizer Animal Health, Kalamazoo, MI) at a dosage of 2 mg/kg, PO q24h. (For additional information on this subject, see Chapter 30.) Methotrexate and cyclophosphamide, two drugs that are commonly administered PO, can also cause anorexia, nausea, and vomiting. Methotrexate commonly causes anorexia and vomiting 2 or 3 weeks after the start of therapy in dogs; these adverse effects are usually controlled with metoclopramide given at the dosage just described. If these problems persist, it may be necessary to discontinue methotrexate treatment. Cyclophosphamide tends to induce anorexia or vomiting in cats. Cyproheptadine (Periactin; Merck Sharp & Dohme, West Point, Pa) at a dosage of 1 to 2 mg (total dose) PO q8-12h is quite effective as an appetite stimulant and antinausea agent in cats.

Gastroenterocolitis is uncommon in animals receiving anticancer agents. Drugs that occasionally cause mucositis include methotrexate, 5-FU, actinomycin D, and doxorubicin. It occurs rarely in association with other alkylating agents, such as cyclophosphamide. Of the drugs mentioned in the previous paragraphs, only doxorubicin and methotrexate appear to be of clinical relevance. On the basis of our experience, Collies and Collie crosses, Old English

Sheepdogs, Cocker Spaniels, and West Highland White Terriers appear to be extremely susceptible to doxorubicininduced enterocolitis.

Doxorubicin-induced enterocolitis is characterized by the development of hemorrhagic diarrhea (with or without vomiting), primarily of the large bowel type, 3 to 7 days after the administration of the drug. Supportive fluid therapy (if necessary) and treatment with therapeutic doses of bismuth subsalicylate-containing products (Pepto-Bismol, 3 to 15 ml or 1-2 tabs PO q8-12h) are generally effective in controlling the clinical signs in dogs, which usually resolve in 3 to 5 days. The administration of Pepto-Bismol from days 1 to 7 of the treatment may alleviate or prevent these signs in dogs at risk for gastroenterocolitis (i.e., one of the breeds mentioned, an animal with a history of this toxicity). The use of bismuth subsalicylate should be avoided in cats. Gastroenteritis associated with the PO administration of methotrexate usually occurs a minimum of 2 weeks after the animal has been receiving this drug; the treatment is the same as that used for doxorubicin-induced enterocolitis.

#### HYPERSENSITIVITY REACTIONS

Acute type I hypersensitivity reactions occasionally occur in dogs receiving parenteral L-asparaginase or doxorubicin and are common in dogs treated with IV etoposide or taxol derivatives; in the latter two, there is a reaction to the solubilizing agent (Tween 80). The reaction to doxorubicin does not appear to be a true hypersensitivity reaction, however, because this agent can induce direct mast cell degranulation independently of immunoglobulin E (IgE) mediation. Etoposide can be safely administered to dogs PO. Hypersensitivity reactions to anticancer agents are extremely rare in cats and thus are not discussed.

Clinical signs in dogs with hypersensitivity reactions to anticancer agents are similar to those in dogs with other types of hypersensitivity reactions (i.e., they are primarily cutaneous and gastrointestinal). Typical signs appear during or shortly after administration of the agent and include head shaking (caused by ear pruritus), generalized urticaria and erythema, restlessness, occasionally vomiting or diarrhea, and rarely collapse caused by hypotension.

Most systemic anaphylactic reactions can be prevented by pretreating the patient with H<sub>1</sub> antihistamines (i.e., IM diphenhydramine, 1 to 2 mg/kg 20 to 30 minutes before administration of the drug) and by administering certain drugs (e.g., L-asparaginase) subcutaneously or intramuscularly rather than through an IV route. If the agent cannot be given by any other routes (i.e., doxorubicin), it should be diluted and administered by slow IV infusion.

The treatment of acute hypersensitivity reactions includes immediate discontinuation of the agent and the administration of H<sub>1</sub> antihistamines (i.e., diphenhydramine, 0.2 to 0.5 mg/kg by slow IV infusion), dexamethasone sodium phosphate (1 to 2 mg/kg IV), and fluids if necessary. If the systemic reaction is severe, epinephrine (0.1 to 0.3 ml of a 1:1000 solution IM or IV) should be used. Once the reaction subsides (and if it was mild), the administration of certain drugs, such as doxorubicin, may be continued. Injectable  $H_1$  antihistamines should be used with caution in cats (if at all), because they can cause acute central nervous system depression leading to apnea.

#### **DERMATOLOGIC TOXICITY**

It is rare for anticancer agents to cause dermatologic toxicity in small animals. However, three types of dermatologic toxicities can occur: local tissue necrosis (caused by extravasation), delayed hair growth and alopecia, and hyperpigmentation.

Local tissue necrosis resulting from the extravasation of vincristine, vinblastine, actinomycin D, or doxorubicin is occasionally seen in dogs receiving these drugs but is extremely rare in cats. Indeed, according to anecdotal reports, cats have accidentally received entire doses of doxorubicin perivascularly without developing tissue necrosis. The pathogenesis of this toxicity is poorly understood, but it is thought to be mediated by release of free radicals; however, some of these drugs are also directly caustic if given perivascularly, causing moderate to severe tissue necrosis. As a consequence, every effort should be made to ensure that these drugs are administered intravascularly. In addition to this complication, some retrievers (e.g., Labrador and Golden Retrievers) appear to experience pruritus or discomfort around the site of the IV injection even when the drug is known to have been administered intravascularly. This pain and discomfort frequently lead to licking and the development of a pyotraumatic dermatitis ("hot spot") within hours of the injection. In these dogs applying a bandage over the injection site or placing an Elizabethan collar prevents this type of reaction.

To prevent or minimize the probability of extravascular injection of caustic drugs, they should be administered through small-gauge (22- to 23-gauge), indwelling, IV, overthe-needle catheters or through 23- to 25-gauge butterfly catheters. We use the former to administer doxorubicin and the latter to administer the vinca alkaloids and actinomycin D. Caustic drugs should be properly diluted before administration (i.e., vincristine to a final concentration of 0.1 mg/ ml and doxorubicin to a concentration of 0.5 mg/ml) and the patency of the intravascular injection site ensured by intermittently aspirating until blood appears in the catheter. In our clinic, we do not administer doxorubicin by IV constant-rate infusion because such patients may be more likely to undergo extravasation. If the site is not patent, the catheter should be placed in another vein. Recommendations for the management of extravascular injections are listed in Box 78-1.

If, despite these precautions, a local tissue reaction occurs, it develops approximately 1 to 7 days after the perivascular injection of vinca alkaloids or actinomycin D and 7 to 15 days after doxorubicin extravasation. Tissue necrosis resulting from doxorubicin extravasation is far more severe than



Recommendations for the Management of Perivascular Injections of Caustic Anticancer Drugs in Cats and Dogs\*

- 1. Do not remove the IV catheter.
- Administer 10 to 50 ml of sterile saline solution through the catheter (in an attempt to dilute the agent).
- With a 25-gauge needle, administer 10 to 20 ml of sterile saline solution subcutaneously in the affected area.
- Inject 1 to 4 mg of dexamethasone sodium phosphate subcutaneously in the affected area (in an attempt to stabilize lysosomal and plasma membranes).
- Apply cold compresses or ice packs to the area for 48 to 72 hours (to cause vasoconstriction and prevent local dissemination of the drug and to decrease local tissue metabolism).

IV, Intravenous.

\* Please see text for additional information.

that associated with the extravasation of other agents because the drug is extremely caustic and persists in tissues for up to 16 weeks. If perivascular administration of doxorubicin has occurred (and the clinician has recognized it during or immediately after the administration), dexrazoxane (Zinecard, Pfizer) can be administered at 5 to 10 times the dose of doxorubicin given (i.e., for 30 mg of doxorubicin, 150-300 mg of dexrazoxane should be given). Dexrazoxane is rather expensive, so it is not routinely used in small animal patients.

We recently evaluated carvedilol (Coreg, Glaxo Smith Kline) in a limited number of dogs that received perivascular doxorubicin. In three dogs that received treatment immediately after drug extravasation (at a dosage of 0.1 to 0.4 mg/kg q12-24h), there were no visible signs of necrosis. In three dogs that developed necrosis after perivascular doxorubicin administration, carvedilol resulted in rapid healing of the area (i.e., within 2-3 weeks).

Clinical signs include pain, pruritus, erythema, moist dermatitis, and necrosis of the affected area; severe tissue sloughing may occur (Fig. 78-2).

If local tissue reactions develop, they can be treated as shown in Box 78-2.

In dogs and cats undergoing chemotherapy delayed hair growth is more common than alopecia. This is in contrast to the situation in human patients, in whom severe scalp alopecia is a predictable complication of therapy. Because most chemotherapeutic agents affect rapidly dividing tissues, cells in the anagen (growth) phase of the hair cycle are usually affected. Therefore hair is slow to regrow in areas that were clipped or shaved before or during chemotherapy. Excessive shedding is also common.

Alopecia occurs predominantly in woolly-haired (coarse-haired) dogs, such as Poodles, Schnauzers, and Kerry Blue Terriers (Fig. 78-3). It affects primarily the tactile hairs in



Tissue necrosis after extravascular injection of doxorubicin in a dog. Note the full-thickness sloughing of the area.



BOX 78-2

#### Treatment of Local Tissue Reactions

- 1. Apply an antibiotic ointment (with or without corticosteroids) to the affected area.
- Bandage the area (and replace bandages daily).
- 3. Prevent self-mutilation by placing an Elizabethan collar or a muzzle.
- 4. If there is no bacterial contamination (ruled out on the basis of negative bacterial cultures), 10 to 20 mg of methylprednisolone acetate (Depo-Medrol; Upjohn-Pharmacia, Kalamazoo, Mich.) can be injected subcutaneously in the affected area to alleviate pruritus and inflammation.
- 5. If severe necrosis or gangrene caused by anaerobic contamination occurs, the area should be surgically debrided.
- 6. In the event of severe doxorubicin-induced soft tissue necrosis, the affected limb may need to be amputated.

short-haired dogs and cats. Although the exact reason that chemotherapy-induced alopecia occurs in woolly-haired dogs is unknown, a prolonged anagen phase and synchronous hair growth, comparable to those occurring in human scalp hair, may make these dogs prone to this toxic effect. Drugs commonly associated with delayed hair growth and alopecia include cyclophosphamide, doxorubicin, 5-FU, 6thioguanine, and hydroxyurea (Hydrea; E.R. Squibb & Sons, Princeton, N.J.). Alopecia and delayed hair growth usually resolve shortly after discontinuation of the offending agent.



FIG 78-3 Alopecia in a 7-year-old Schnauzer undergoing doxorubicin and dacarbazine (ADIC) chemotherapy. Note the short and light-colored haircoat.

Hyperpigmentation is uncommon in dogs and extremely rare in cats receiving chemotherapy. Cutaneous hyperpigmentation affecting the face, ventral abdomen, and flanks is common in dogs receiving doxorubicin- and bleomycincontaining protocols.

#### **PANCREATITIS**

Pancreatitis is a well-recognized entity in human patients undergoing chemotherapy. Offending drugs in humans include corticosteroids, azathioprine, 6-mercaptopurine, L-asparaginase, cytosine arabinoside, and combination chemotherapy. Sporadic reports of pancreatitis in dogs (but not in cats) receiving chemotherapeutic and immunosuppressive agents have also appeared in the literature.

We have documented acute pancreatitis in several dogs receiving 1-asparaginase or combination chemotherapy. Dogs in the latter group were receiving COAP (cyclophosphamide, vincristine, cytosine arabinoside, prednisone), ADIC (doxorubicin, DTIC); or VAC (vincristine, doxorubicin, cyclophosphamide) chemotherapy. Clinical signs developed 1 to 5 days after the start of chemotherapy and consisted of anorexia, vomiting, and depression. Physical examination findings in these dogs were unremarkable, and abdominal pain was rare. Serum lipase and amylase activities were high in all the animals, and ultrasonographic evidence of pancreatitis was detected in approximately one half of the dogs. The animals were treated with IV fluids, and the clinical signs resolved within 3 to 10 days in most dogs.

It is difficult to prevent chemotherapy-induced pancreatitis because it is not a predictable complication. As a general precaution, we refrain from using L-asparaginase in dogs at high risk for pancreatitis (i.e., overweight middle-age to older female dogs). As a further precaution, dogs receiving drugs with the potential to cause pancreatitis should be fed a low-fat diet.

#### **CARDIOTOXICITY**

Cardiotoxicity is a relatively uncommon complication of doxorubicin therapy in dogs; it is extremely rare in cats. Two types of doxorubicin-induced cardiac toxicity are observed in dogs: an acute reaction occurring during or shortly after administration and a chronic cumulative toxicity. Acute doxorubicin toxicity is characterized by cardiac arrhythmias (mainly sinus tachycardia) that develop during or shortly after administration. This phenomenon is thought to stem from doxorubicin-induced, histamine-mediated catecholamine release because the sinus tachycardia and hypotension can be prevented by pretreatment with H1 and H2 antihistamines. Several weeks or months after repeated doxorubicin injections, persistent arrhythmias, including ventricular premature contractions, atrial premature contractions, paroxysmal ventricular tachycardia, second-degree atrioventricular blocks, and intraventricular conduction defects, develop. These rhythm disturbances are usually associated with the development of a dilated cardiomyopathy, similar to that which occurs spontaneously in Doberman Pinschers and Cocker Spaniels.

The hallmark of chronic doxorubicin toxicity is a dilated cardiomyopathy that develops after a total cumulative dose of approximately 240 mg/m² is exceeded in the dog. The histologic lesions seen in dogs with doxorubicin-induced cardiomyopathy consist of vacuolation of myocytes, with or without myofibril loss. Clinical signs of toxicity in dogs are those of congestive heart failure (usually left-sided). Therapy consists of discontinuation of the offending drug and the administration of cardiac drugs such as digitalis glycosides or nonglycoside inotropic agents. Once cardiomyopathy develops, the prognosis is poor because the myocardial lesions are irreversible.

It is critical to monitor patients receiving doxorubicin to prevent fatal cardiomyopathy. In this respect, dogs (and possibly) cats with underlying rhythm disturbances or impaired myocardial contractility, as shown by decreased fractional shortening on M-mode or Doppler echocardiograms, should not receive doxorubicin. It is also recommended that animals receiving doxorubicin undergo echocardiographic evaluation every three doxorubicin cycles (9 weeks) to assess myocardial contractility and that the drug be discontinued if decreased fractional shortening occurs. Endomyocardial biopsy specimens are commonly obtained in people receiving doxorubicin in an effort to detect submicroscopic lesions, but this is impractical in dogs. The value of serum cardiac troponin I concentrations to detect early myocardial damage from doxorubicin is currently being evaluated in dogs.

Several protocols have been devised in an attempt to minimize doxorubicin-induced cardiomyopathy in dogs. Unfortunately, only two have shown promise in minimizing or preventing cardiomyopathy. Of these, weekly low-dose doxorubicin therapy in humans has been found to be associated with a significantly lower frequency of histologic changes than the conventional 3-week schedule has been. I have been

able to administer total cumulative doses of 500 mg/m² to two dogs using a 10 mg/m² weekly protocol. However, recent reports describe a loss of antitumor activity when using weekly low-dose doxorubicin in dogs with lymphoma. A new compound, dexrazoxane (Zinacard, Upjohn-Pharmacia, Kalamazoo, Mich.), offers a promising means of reducing the chronic cardiotoxicity induced by doxorubicin; doses in excess of 500 mg/m² have been administered to dogs receiving the agent without causing significant cardiotoxicity. Recently, carvedilol (0.1-0.4 mg/kg, PO, q12-24h) has been used successfully to prevent or decrease the probability of developing doxorubicin-associated cardiomyopathy in people (Kalay et al, 2006); we have successfully used carvedilol in dogs with subclinical myocardial dysfunction that needed doxorubicin.

#### UROTOXICITY

The urinary tract in small animals is rarely affected by adverse reactions to anticancer agents. Only two specific complications are of clinical importance in pets with cancer: nephrotoxicity and sterile hemorrhagic cystitis. Transitional cell carcinomas of the urinary bladder associated with chronic cyclophosphamide therapy have also been reported in dogs.

Nephrotoxicity is rarely observed in dogs and cats undergoing chemotherapy. Although several potentially nephrotoxic drugs are commonly used in these species, only doxorubicin (primarily in cats), cisplatin (in dogs), and intermediate to high doses of methotrexate (in dogs) are of concern to clinicians. In our clinic we do not use cisplatin frequently on account of its potential to induce nephrotoxicity.

Doxorubicin may be a nephrotoxin in cats, and the limiting cumulative toxicity in this species may be renal rather than cardiac. Doxorubicin may cause nephrotoxicosis in dogs with preexisting renal disease and in those concomitantly receiving other nephrotoxins, such as aminoglycoside antibiotics or cisplatin. The administration of cisplatin using forced diuresis protocols minimizes the prevalence of nephrotoxicity in dogs.

Sterile hemorrhagic cystitis is a relatively common complication of long-term cyclophosphamide therapy in dogs; rarely, it may also occur acutely after a single dose of cyclophosphamide. This toxicity is not clinically relevant in cats. Acute clinical signs and urinalysis changes compatible with sterile hemorrhagic cystitis developed after the first injection in three dogs treated at our clinic with IV cyclophosphamide, 100 mg/m², and four dogs receiving PO cyclophosphamide, 300 mg/m². Sterile cystitis results from the irritating effects of one of the cyclophosphamide metabolites (acrolein). It develops in approximately 5% to 25% of dogs and 1% to 3% of cats treated with cyclophosphamide, usually after an average of 18 weeks of therapy. Furosemide or prednisone administered concomitantly with cyclophosphamide appears to decrease the prevalence of cystitis.

Forced diuresis appears to minimize the severity of this complication or prevent it. I usually recommend administering the cyclophosphamide in the morning, allowing the pet to urinate frequently (if it is an indoor dog), salting the food, and administering prednisone on the same day that the animal receives the cyclophosphamide (if the protocol calls for prednisone administration).

Clinical signs of sterile hemorrhagic cystitis are similar to those of other lower urinary tract disorders and include pollakiuria, hematuria, and dysuria. Urinalysis typically reveals blood and mildly to moderately increased numbers of white blood cells but no bacteria. Treatment of this complication consists of discontinuing the cyclophosphamide, forcing diuresis, diminishing the inflammation of the bladder wall, and preventing secondary bacterial infections. The cystitis resolves in most dogs within 1 to 4 months after the cyclophosphamide is discontinued. I administer furosemide (Lasix) at a dosage of 2 mg/kg PO every 12 hours for its diuretic effects, prednisone at a dosage of 0.5 to 1 mg/kg PO every 24 hours for its antiinflammatory (and diuretic) effect, and an ST combination at a dose of 13 to 15 mg/kg PO every 12 hours to prevent secondary bacterial contamination. If the clinical signs worsen despite this approach, the instillation of 1% formalin solution in water into the bladder can be attempted. Gross hematuria resolved within 24 hours and did not recur in two dogs thus treated. The intravesical infusion of a 25% to 50% dimethylsulfoxide solution may also alleviate the signs of cystitis in dogs.

#### HEPATOTOXICITY

Chemotherapy-induced hepatotoxicity is extremely rare in dogs and cats. With the exception of the hepatic changes induced by corticosteroids in dogs, to my knowledge only methotrexate, cyclophosphamide, lomustine, and azathioprine (Imuran; Burroughs Wellcome, Research Triangle Park, N.C.) have been implicated as or confirmed to be hepatotoxins in dogs. In my experience, the hepatotoxicity caused by anticancer drugs in small animals is of little or no clinical relevance, with the exception of lomustine.

A recent report describes a low prevalence of hepatotoxicity (<10%) in dogs receiving lomustine (CCNU) for lymphoma or mast cell tumors. In our clinic we have documented marked increases in alanine transaminase (ALT) activities (>1000 IU/L) and mild increases in alkaline phosphatase (ALP) activities (<500 IU/L) within 3 weeks of starting lomustine therapy in several dogs with mast cell tumors or granulomatous meningoencephalitis. Most dogs had decreases in the ALT and ALP concentrations after lengthening the dosing interval, decreasing the individual dosage, or both. In my experience, hepatoprotectors appear to be of no benefit in preventing CCNU-induced hepatotoxicity.

Dogs with immune-mediated disorders receiving chronic azathioprine therapy rarely develop increases in liver enzyme activities that respond to discontinuation of the drug.

# **NEUROTOXICITY**

Anticancer agent-induced neurotoxicity is also extremely rare in dogs and cats. Neurotoxicosis occurs infrequently in dogs receiving 5-FU, although it is common in cats (for this reason, this drug should not be used in cats). Neurotoxicity can also occur in dogs and cats that ingest 5-FU intended for human use (i.e., prescribed for the owners). Clinical signs occur shortly (3 to 12 hours) after ingestion of the drug and consist primarily of excitation and cerebellar ataxia, resulting in death in approximately one third of the dogs and in most cats. Neurotoxicity was also documented in 25% of dogs receiving a combination of actinomycin D, 5-FU, and cyclophosphamide (the CDF protocol) for the management of metastatic or nonresectable carcinomas at our clinic. This prevalence is considerably higher than that seen in association with the use of 5-FU in combination with other drugs and may be a result of drug interactions.

# **PULMONARY TOXICITY**

Pulmonary toxicity is extremely rare in dogs and cats receiving chemotherapy. To my knowledge, only cisplatin has been documented as a cause of pulmonary toxicity in cats. Acute signs of dyspnea leading to death occur within 48 to 96 hours of the administration of cisplatin in this species. Necropsy findings consist of pulmonary and mediastinal edema and microangiopathic changes in the pulmonary vasculature. Because of the risk of this serious toxicity, cisplatin should not be used in cats; carboplatin, a cisplatin derivative, does not cause pulmonary toxicity in this species.

# **ACUTE TUMOR LYSIS SYNDROME**

In human patients the rapid lysis of certain tumor cells (e.g., lymphoma cells) shortly after chemotherapy may lead to a syndrome of hyperuricemia, hyperphosphatemia, and hyperkalemia, either singly or in combination. This clinical entity is referred to as *acute tumor lysis syndrome* and is thought to be secondary to the release of high quantities of intracellular phosphate, uric acid, and nucleic acid metabolites. The intracellular concentration of phosphorus in human lymphoma and leukemic cells is four to six times higher than that in normal lymphocytes, and the same appears to be true for dogs.

In dogs ATLS has been reported to occur only in association with lymphomas treated with chemotherapy, radiation therapy, or both and is characterized by hyperphosphatemia, with or without azotemia, hyperkalemia, hypocalcemia, metabolic acidosis, and hyperuricemia. It is rare in cats. Clinical signs include depression, vomiting, and diarrhea and occur within hours of the start of chemotherapy.

We have documented clinically evident ATLS after chemotherapy in 10 dogs with lymphoma, during a period in

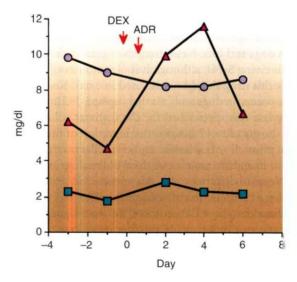


FIG 78-4

Serum phosphorus ( ), calcium ( ), and creatinine ( ) concentrations in a dog with acute tumor lysis syndrome after chemotherapy for a primary pulmonary lymphoma. Note the increase in the serum phosphorus concentrations, with a mild decrease in the calcium concentrations and minor increases in the serum creatinine concentrations. DEX, Dexamethasone; ADR, doxorubicin. (From Couto CG: Management of complications of cancer chemotherapy, Vet Clin North Am 20:1037, 1990.)

which approximately 2000 dogs with lymphoma were treated with chemotherapy. In most dogs the pretreatment serum creatinine concentrations or the tumor burden was high; one of the dogs had high liver enzyme activities. Within 1 to 7 days of the start of chemotherapy, lethargy, vomiting, and

bloody diarrhea developed in affected dogs and the serum phosphorus concentrations increased markedly (Fig. 78-4). Aggressive fluid therapy and the correction of acid-base and electrolyte disturbances resulted in resolution of the clinical signs within 3 days in six dogs; the remaining two dogs died as a result of ATLS.

# **Suggested Readings**

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# CHAPTER Approach to the Patient with a Mass

# CHAPTER OUTLINE

APPROACH TO THE CAT OR DOG WITH A SOLITARY MASS

APPROACH TO THE CAT OR DOG WITH A METASTATIC LESION

APPROACH TO THE CAT OR DOG WITH A MEDIASTINAL MASS

# APPROACH TO THE CAT OR DOG WITH A SOLITARY MASS

It is common for the practicing veterinarian to evaluate a clinically healthy cat or dog in which a single mass is found during a routine physical examination or in which the owner has detected a mass and is concerned about it. The mass can be superficial (e.g., enlarged prescapular lymph node, subcutaneous mass) or deep (e.g., splenic mass, enlarged mesenteric lymph node), and often the clinician wonders how to proceed and what to recommend to the owner.

In this situation there are several possible approaches:

- 1. Do nothing and see if the mass "goes away."
- 2. Evaluate the mass cytologically.
- 3. Evaluate the mass histopathologically.
- 4. Do a complete workup, including complete blood count (CBC), serum biochemistry profile, radiography, abdominal ultrasonography, and urinalysis.

The first option (i.e., do nothing and see if the mass goes away) is not really an option because the presence of any mass is abnormal, and it should therefore be evaluated. As a general rule, most masses, with the notable exception of inflammatory lesions, histiocytomas in young dogs, and transmissible venereal tumors, do not regress spontaneously.

At our clinic the typical first step in evaluating a solitary mass is to perform fine-needle aspiration (FNA) to obtain material for cytologic evaluation (see Chapter 75). Using this simple, relatively atraumatic, quick, and inexpensive procedure, the clinician can arrive at a highly presumptive or definitive diagnosis in the vast majority of animals. After identifying the nature of the mass (i.e., benign neoplastic, malignant neoplastic, inflammatory, or hyperplastic), the clinician can recommend additional tests to the owner.

Performing a biopsy for histopathology constitutes another valid alternative. However, the cost, the trauma to the patient, and the time it takes for the pathologist's report to become available make this a less attractive option than FNA. An intensive workup of a cat or dog with a solitary mass (i.e., option 4) may not be warranted because additional diagnostic information regarding the mass is rarely gained from these procedures. However, the presence of metastatic lesions on thoracic radiographs may suggest that the mass in question is a malignant tumor.

If a cytologic diagnosis of a benign neoplasm is made (e.g., lipoma), the clinician faces two options: to do nothing and observe the mass or to surgically excise it. Because benign neoplasms in cats and dogs are rarely premalignant (with the notable exception of solar dermatitis/carcinoma in situ preceding the development of squamous cell carcinomas in cats), if a benign neoplasm is definitively diagnosed, a sound approach is to recommend a wait-and-see attitude. If the mass enlarges, becomes inflamed, or ulcerates, then surgical excision is recommended. However, the clinician should keep in mind that most benign neoplasms are more easily excised when they are small (i.e., it is not advisable to wait until the mass becomes quite large). To some owners the option of surgically excising the mass shortly after diagnosis is more appealing.

If a cytologic diagnosis of malignancy is obtained (or if the findings are suggestive of or compatible with malignancy), additional evaluation is warranted. Different approaches are indicated, depending on the cytologic diagnosis (i.e., carcinoma versus sarcoma versus round cell tumor). However, with the exception of mast cell tumors (i.e., pulmonary metastases are extremely rare in dogs and cats with this tumor type), thoracic radiographs should be obtained to search for metastatic disease in dogs and cats with most types of malignant neoplasms. Two lateral views

and a ventrodorsal (or dorsoventral) view are recommended to increase the likelihood of detecting metastatic lesions. If available, a computed tomography (CT) scan may be obtained because it can detect masses smaller than those detectable on plain radiography. Plain radiographs of the affected area may also be indicated to look for soft tissue and bone involvement. Abdominal ultrasonography (or radiography) may be indicated for further staging in animals with certain neoplasms (e.g., hemangiosarcoma, intestinal neoplasms, mast cell tumors). A CBC, serum biochemistry profile, and urinalysis may provide additional clinical information (e.g., paraneoplastic syndromes, concurrent organ failure).

If the mass is malignant and there is no evidence of metastatic disease, surgical excision is usually recommended. If there are metastatic lesions, the pathologist feels comfortable with the cytologic diagnosis, and the tumor is likely to respond to chemotherapy (e.g., lymphoma, hemangiosarcoma), chemotherapy constitutes the best viable option (see Chapter 76). However, as discussed in Chapter 76, surgical resection of the primary mass (e.g., mammary carcinoma) in a patient with metastatic lesions may provide considerable palliation and prolong good-quality survival. If an assertive diagnosis cannot be made on the basis of the cytologic findings, an incisional or excisional biopsy of the mass is advisable. In our clinic we typically do not recommend euthanasia in dogs and cats with metastatic lesions and good quality of life because survival times in excess of 6 months (without chemotherapy) are common in animals with most metastatic neoplasms.

# APPROACH TO THE CAT OR DOG WITH A METASTATIC LESION

Radiographic or ultrasonographic evidence of metastatic cancer is often found during the routine evaluation of an animal with a suspected or confirmed malignancy or during the evaluation of a cat or dog with obscure clinical signs. In such instances the clinician should be familiar with both the biologic behavior of the common neoplasms and with their characteristic radiographic and ultrasonographic patterns (Table 79-1). Suter et al. (1974) have described the typical radiographic appearances of various metastatic malignancies. In addition, the owner should be questioned regarding any prior surgeries in the pet (e.g., excision of a mass that was thought to be benign but may have been the primary malignancy).

If a cytologic or histopathologic diagnosis of malignancy has already been made and the metastatic lesions are detected while staging the animal, treatments can be recommended to the owner at this point (assuming that the metastatic lesions have arisen from the previously diagnosed primary tumor). As a general rule, cytologic or histopathologic evaluation of one or more of these lesions should be performed so that the clinician can best advise the owner as to the appropriate course of action.

A cytologic diagnosis of metastatic lung lesions can usually be obtained through blind or ultrasonography-, fluoroscopy-, or CT-guided percutaneous FNA of the lungs. To do this, the area to be aspirated (i.e., the one with the highest density of lesions radiographically or the identified lesions) is clipped and aseptically prepared. For blind percutaneous lung aspirates the animal should be in sternal recumbency or standing; a 25-gauge, 2- to 3-inch (5- to 7.5-cm) needle (depending on the size of the animal) coupled to a 12- to 20-ml syringe is rapidly advanced through an intercostal space along the cranial border of the rib to the depth required (previously determined on the basis of the radiographs), and suction is applied two or three times and then released; the needle is then withdrawn. Smears are made as described in Chapter 75. When aspirating lungs, the clinician is likely to obtain a fair amount of air or blood (or both) in the syringe. Rare complications associated with this technique include pneumothorax (animals should be closely observed for 2 to 6 hours after the procedure and dealt with accordingly if pneumothorax

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TABLE 79-1

Metastatic Behavior of Some Common Neoplasms in Dogs and Cats

NEOPLASM	SPECIES	COMMON METASTATIC SITES
HSA	D	Liver, lungs, omentum, kidney, eye, CNS
OSA	D	Lungs, bone
SCC—oral	C, D	Lymph nodes, lungs
aCA-mammary	C, D	Lymph nodes, lungs
aCA—anal sac	D	Lymph nodes
aCA—prostate	D	Lymph nodes, bone, lungs
TCC-bladder	D	Lymph nodes, lungs, bone
MEL—oral	D	Lymph nodes, lungs
MCT	D	Lymph nodes, liver, spleen
MCT	С	Spleen, liver, bone marrow

develops) and bleeding. As a general rule, FNA of the lungs should not be performed in cats or dogs with coagulopathies.

If an FNA of the lungs fails to yield a diagnostic sample, a lung biopsy performed with a biopsy needle (under ultrasonographic, fluoroscopic, or CT guidance) or through a thoracotomy should be contemplated. This procedure is associated with an extremely low morbidity and should be recommended if owners are considering treatment.

Metastatic lesions in other organs or tissues (e.g., liver, bone) can also be diagnosed on the basis of FNA findings. The clinician should remember that nodular lesions of the liver or spleen in dogs with a primary malignancy should not necessarily be considered metastatic. FNA or biopsies of such lesions frequently reveal normal hepatocytes (i.e., regenerative hepatic nodule) or extramedullary hematopoiesis/lymphoreticular hyperplasia, respectively. In the case of bone metastases, an aspirate can be obtained using a hypodermic needle (20-22G) that is inserted blindly or under ultrasonographic guidance; if this fail to yield cells, a 16 or 18 gauge bone marrow aspiration needle can be used. If a cytologic diagnosis cannot be made, a core (needle) biopsy can be performed.

As discussed in Chapter 76, cats and dogs with metastatic neoplasms can now be treated fairly successfully using chemotherapy. To do this, however, it is necessary to know the histologic (or cytologic) tumor type. The clinician should always bear in mind that euthanasia is a viable option for some owners.

# APPROACH TO THE CAT OR DOG WITH A MEDIASTINAL MASS

Several lesions are found as anterior mediastinal masses (AMMs) during physical examination or plain thoracic radiography (Table 79-2). Some of these lesions are malignant neoplasms; therefore diagnosis and treatment should be approached aggressively in such animals.

# Clinicopathologic Features and Diagnosis

When evaluating a cat or dog with an AMM, the clinician should consider several issues before recommending a

specific treatment. As discussed previously (see Chapter 76), the treatment prescribed depends on the specific tumor type (i.e., surgical excision may be curative for dogs and cats with thymomas, whereas chemotherapy is indicated for those with lymphoma). Because lymphomas and thymomas are the most common AMMs in small animals, the ensuing discussion is limited to these two neoplasms. Other neoplasms that originate in anterior mediastinal structures include chemodectomas (heartbase tumors), ectopic thyroid carcinomas, and lipomas, among others. Nonneoplastic lesions of the mediastinum include mainly thymic or mediastinal hematomas and ultimobranchial cysts.

Paraneoplastic syndromes, such as generalized or focal myasthenia gravis, polymyositis, exfoliative dermatitis, and second neoplasms, have been well characterized in cats and dogs with thymoma. Aplastic anemia, a paraneoplastic syndrome common in humans with thymoma, has not been recognized in small animals with this tumor type. Hypercalcemia is a common finding in dogs with mediastinal lymphoma, but it can also occur in dogs with thymoma.

In cats the age at the time of presentation points to a specific diagnosis. In other words, anterior mediastinal lymphomas are more common in young cats (1 to 3 years old), whereas thymomas are more common in older cats (8 to 10 years old). It is also important to know the feline leukemia virus (FeLV) status in this species because most cats with mediastinal lymphomas are viremic (i.e., FeLV-positive), whereas most cats with thymoma are not. We occasionally see FeLV-negative mediastinal lymphomas in young to middle-age Siamese cats.

In dogs most AMMs are diagnosed in older animals (older than 5 to 6 years of age); therefore age cannot be used as a means of distinguishing between lymphomas and thymomas. However, a large proportion of dogs with mediastinal lymphomas are hypercalcemic, whereas most dogs with thymoma are not (although hypercalcemia can also occur in dogs with this neoplasm). Peripheral lymphocytosis can be present in dogs and cats with either lymphoma or thymoma. The presence of neuromuscular signs in a dog or cat with an AMM suggests the existence of a thymoma.

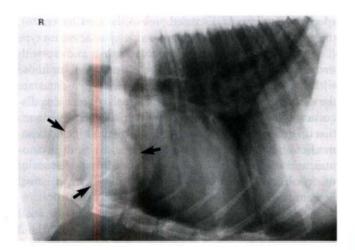


**TABLE 79-2** 

Anterior Mediastinal Masses in Cats and Dogs

LESION	CAT	DOG	COMMENTS
Thymoma	Common	Common	See text
Lymphoma	Common	Common	See text
Thyroid adenocarcinoma	Rare	Rare	
Lipoma	Rare	Rare	Low radiographic density
Branchial cysts	Rare	Rare	Cystic on ultrasound
Thymic hematomas	ŝ	Rare	Traumatic, rodenticides?
Heartbase tumors	ŝ	Rare	Brachiocephalic breeds

<sup>?,</sup> Questionable.



Typical radiographic features of thymoma (arrows) in a dog. The mass originates in the ventral mediastinum, unlike most lymphomas, which usually originate in the dorsal mediastinal region. Percutaneous fine-needle aspiration of this mass yielded findings diagnostic for thymoma, and the

mediastinal region. Percutaneous tine-needle aspiration of this mass yielded findings diagnostic for thymoma, and the dog underwent a thoracotomy with complete resection of the mass.

Thoracic radiographs are of little help in differentiating thymomas from lymphomas. The two neoplasms are similar in appearance, although lymphomas appear to originate more frequently in the dorsal anterior mediastinum, whereas thymomas originate more often in the ventral mediastinum (Fig. 79-1). The prevalence of pleural effusion in dogs and cats with either thymomas or lymphomas appears to be similar; thus the finding cannot be used as a means to distinguish between these two tumor types.

Ultrasonographic evaluation of the AMM should be attempted before more invasive diagnostic techniques are used. Ultrasonographically, most thymomas have a mixed echogenicity, with discrete hypoechoic to anechoic areas that correspond to true cysts on cross section. The lack of a supporting stroma in lymphomas usually confers a hypoechoic to anechoic density to the mass, which therefore may look diffusely cystic. In addition to aiding in the presumptive diagnosis of a given tumor type, ultrasonography may provide information regarding the resectability of the mass and assists in obtaining a specimen for cytologic evaluation (see next paragraph). In patients with thymoma a thoracic CT scan may help in planning surgery.

Transthoracic FNA of AMMs constitutes a relatively safe and reliable evaluation technique. After sterile preparation of the thoracic wall overlying the mass (see Chapter 75), a 2- to 3-inch (5- to 7.5-cm), 25-gauge needle coupled to a syringe is used to aspirate the mass. This can be done blindly (if the mass is so large that it is pressing against the interior thoracic wall) or guided by radiography (using three views to establish a three-dimensional location), fluoroscopy, ultrasonography, or CT. Despite the fact that there are large vessels within the anterior mediastinum, postaspiration bleeding is extremely rare if the animal remains motionless

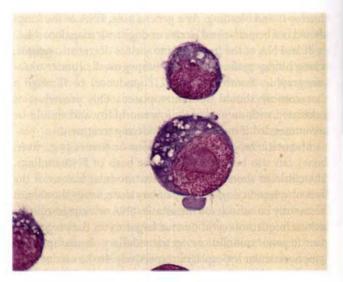


FIG 79-2 Cytologic characteristics of feline mediastinal lymphoma. Note the dark cytoplasm with abundant vacuoles typical of this neoplasm in cats. (×1000.)

during the procedure. Alternatively, if the mass is large enough to be in close contact with the internal thoracic wall, a transthoracic needle biopsy can be performed to allow histopathologic evaluation.

Cytologically, mediastinal lymphomas are composed of a monomorphic population of lymphoid cells that are mostly immature (i.e., low nuclear-to-cytoplasmic ratio, dark blue cytoplasm, clumped chromatin pattern, and nucleoli); in cats most cells in anterior mediastinal lymphomas are heavily vacuolated and resemble human Burkitt's lymphoma cells (Fig. 79-2). Thymomas are cytologically heterogeneous and composed primarily of a population of small lymphocytes (although large blasts are sometimes present), and occasionally a distinct population of epithelial-like cells that are usually polygonal or spindle shaped and can be identified either as individual cells or in sheets. Hassall's corpuscles are rarely seen in Wright's-stained cytologic preparations. Plasma cells, eosinophils, neutrophils, mast cells, macrophages, and melanocytes are all occasionally seen.

#### **Treatment**

As discussed in preceding paragraphs, anterior mediastinal lymphomas are best treated with chemotherapy (see Chapter 80). Radiotherapy can also be used in conjunction with chemotherapy to induce a more rapid remission. However, in my experience, the combination of radiotherapy and chemotherapy does not offer any advantages over chemotherapy alone, and it may indeed be detrimental to the animal, given that many cats and dogs with anterior mediastinal lymphoma have severe respiratory compromise at the time of presentation. Chemical restraint of these animals for radiotherapy may further compound this problem.

Because most thymomas are benign, surgical excision is usually curative. Although in some reports the perioperative

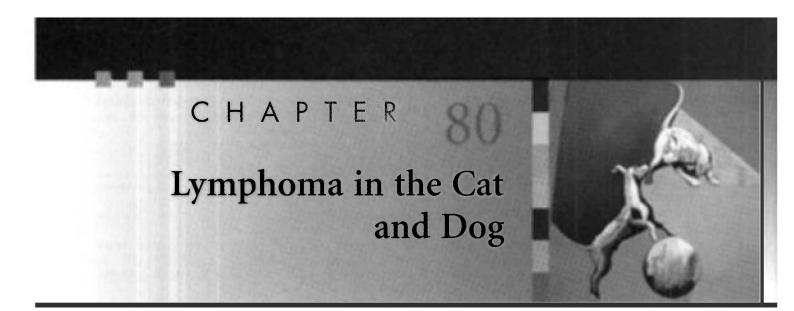
morbidity and mortality of this procedure are high (Atwater et al., 1994), in our experience, most patients that undergo thoracotomies for removal of a thymoma do well and are released from the hospital in 3 to 4 days. We recently reviewed the surgical outcome in 9 cats and 11 dogs with thymomas (Zitz et al., 2008); eight out of nine cats and eight out of eleven dogs survived the immediate postoperative period and had median survival times of 30 and 18.5 months, respectively. Two cats and one dog had late recurrences.

Radiotherapy can successfully induce remission in patients with thymoma, although complete, long-lasting remission is rarely achieved. This may be because the radiotherapy eliminates only the lymphoid component of the neoplasm but the epithelial component remains unchanged. Chemotherapy may be beneficial in selected cats and dogs with nonresectable thymomas or in those in which repeated anesthetic episodes or a major surgical procedure poses a severe risk. We have used combination chemotherapy protocols commonly used for dogs and cats with lymphoma (i.e., cyclophosphamide, vincristine, cytosine arabinoside, and prednisone [COAP]; cyclophosphamide, vincristine, and prednisone [COP]; and cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; see Chapter 80) in a limited number of cats and dogs with cytologically diagnosed thymomas. As with radiotherapy, however, chemotherapy may only eliminate the lymphoid cell population, thus rarely resulting in complete or long-lasting remissions.

If a definitive diagnosis of thymoma or lymphoma cannot be obtained preoperatively, the clinician has two therapeutic options: (1) to perform a thoracotomy and excise the mass or (2) to initiate chemotherapy for lymphoma (COP, COAP, or CHOP). In the latter case, if no remission (or only a partial remission) is observed 10 to 14 days after the start of chemotherapy, the mass is most likely a thymoma and surgical resection should be considered.

# Suggested Readings

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# CHAPTER OUTLINE

Etiology and Epidemiology Clinical Features Diagnosis Treatment

Lymphoma (i.e., malignant lymphoma, lymphosarcoma) is a lymphoid malignancy that originates from solid organs (e.g., lymph nodes, liver, spleen); this distinguishes lymphomas from lymphoid leukemias, which originate in the bone marrow (see Chapter 81).

# **Etiology and Epidemiology**

Early reports stated that approximately 70% of cats with lymphoma have feline leukemia virus (FeLV) infection (Table 80-1). Although the prevalence of viremia in cats with lymphoma varies with the anatomic form of presentation (see later discussion), young cats with lymphoma generally are FeLV-positive, whereas older cats are FeLV-negative. Over the past few years, the prevalence of FeLV infection in cats with lymphoma seen at our clinic has been decreasing. Feline immunodeficiency virus (FIV) infection increases the risk of developing lymphoma in cats; cats infected with FIV are almost six times more likely to develop lymphoma than noninfected cats, whereas cats coinfected with FeLV and FIV are more than 75 times more likely to develop lymphoma than noninfected cats (Shelton et al., 1990). Recently, Louwerens et al. (2005) reported an increase in the prevalence of feline lymphoma, despite the decrease in the prevalence of FeLV infection; this increase was associated with a high prevalence of the gastrointestinal form, extranodal or atypical forms, and FeLV-negative mediastinal forms in young to middle-aged Siamese and oriental breeds.

In dogs the etiology of lymphomas is considered multifactorial because no single etiologic agent has been identified. However, a genetic component is evident, in that the neoplasm is highly prevalent in certain breeds and bloodlines (Modiano et al., 2005). There is also a distinct breedrelated predisposition to lymphoma in dogs, with some breeds, such as the Boxer, Basset Hound, Rottweiler, Cocker Spaniel, Saint Bernard, Scottish Terrier, Airedale Terrier, English Bulldog, and Golden Retriever, being at high risk. At our clinic the breeds most commonly affected are Golden Retrievers, Cocker Spaniels, and Rottweilers.

The age of cats with lymphoma at the time of presentation is bimodal, with the first peak occurring in cats that are approximately 2 years of age and the second one occurring in cats that are approximately 10 to 12 years of age. The cats that make up the first peak are mainly FeLV-positive, whereas those that make up the second peak are predominantly FeLV-negative. As mentioned before, the prevalence of FeLV-positive cats with lymphoma continues to decrease at our clinic. The mean age of FeLV-positive cats with lymphoma when first seen is 3 years, whereas the mean age of FeLV-negative cats with lymphoma is 7 to 8 years. Most dogs with lymphoma are middle-age or older (6 to 12 years of age).

#### **Clinical Features**

There are four anatomic forms of presentation in cats and dogs with lymphoma:

- 1. *Multicentric*, characterized by generalized lymphadenopathy; hepatic, splenic, or bone marrow involvement; or a combination of these
- 2. *Mediastinal*, characterized by mediastinal lymphadenopathy, with or without bone marrow infiltration
- 3. Alimentary, characterized by solitary, diffuse, or multifocal gastrointestinal tract infiltration, with or without intraabdominal lymphadenopathy
- 4. *Extranodal*, affecting any organ or tissue (e.g., renal, neural, ocular, cutaneous)

The distribution of the different anatomic forms differs between cats and dogs. The multicentric form is the most common in dogs, accounting for more than 80% of all the lymphomas in this species. In cats the alimentary form is the most common. At our clinic, alimentary lymphoma is found in more than 70% of the cats with this neoplasm.

The clinical findings in cats and dogs with lymphoma are related to the anatomic form of the presentation. Animals with the generalized or multicentric form are evaluated because of vague, nonspecific clinical signs; frequently, the owners detect one or more subcutaneous masses (i.e., enlarged lymph nodes) during grooming in an otherwise healthy pet, and this prompts them to seek veterinary care. Occasionally, dogs and cats with lymphoma are evaluated because of nonspecific clinical signs, such as weight loss, anorexia, and lethargy. If the enlarged lymph nodes mechanically obstruct lymphatic drainage, edema occurs; if they compress the airway, coughing is the main presenting complaint.

Physical examination of cats and dogs with multicentric lymphoma usually reveals massive generalized lymphade-nopathy, with or without hepatomegaly, splenomegaly, or extranodal lesions (e.g., ocular, cutaneous, renal, neural). The affected lymph nodes are markedly enlarged (5 to 15 times their normal size), painless, and freely movable. A syndrome of reactive (hyperplastic) lymphadenopathy that occurs in cats can mimic the clinicopathologic features of multicentric lymphoma.

Cats and dogs with mediastinal lymphoma are usually evaluated because of dyspnea, coughing, or regurgitation (the latter is more common in cats) of recent onset. Polyuria and polydipsia are common presenting complaints in dogs with mediastinal lymphoma and hypercalcemia; tumorassociated hypercalcemia is extremely rare in cats with lymphoma. The respiratory and upper digestive tract signs are



TABLE 80-1

Prevalence of Feline Leukemia Virus Infection in Cats with Lymphoma

ANATOMIC FORM	FeLV POSITIVE (%)
Alimentary	30
Mediastinal	90
Multicentric	80
Cutaneous	0

caused by compression from enlarged anterior mediastinal lymph nodes, although malignant pleural effusion can contribute to the severity of the respiratory tract signs. On physical examination the abnormalities are usually confined to the thoracic cavity and consist of decreased bronchovesicular sounds, normal pulmonary sounds displaced to the dorsocaudal thoracic cavity, a dull sound heard on percussion of the ventral thoracic cavity, and a noncompressible anterior mediastinum (in cats). Unilateral or bilateral Horner's syndrome may occur in cats (and occasionally dogs) with mediastinal lymphoma. Some dogs with mediastinal lymphoma have marked head and neck edema caused by compression from enlarged lymph nodes (anterior vena cava syndrome).

Cats and dogs with an alimentary lymphoma usually display gastrointestinal tract signs, such as vomiting, anorexia, diarrhea, and weight loss. Occasionally, signs compatible with an intestinal obstruction or peritonitis (caused by rupture of a lymphomatous mass) occur. Physical examination typically reveals an intraabdominal mass or masses (e.g., enlarged mesenteric or ileocecocolic lymph nodes or intestinal masses) and thickened bowel loops (in patients with diffuse small intestinal lymphoma). Rarely, polypoid lymphomatoid masses can protrude through the anus in dogs with colorectal lymphoma.

The clinical signs and physical examination findings in cats and dogs with extranodal lymphomas are extremely variable and depend on the location of the mass or masses. In general, the clinical signs stem from the compression or displacement of normal parenchymal cells in the affected organ (e.g., azotemia in renal lymphoma, variable neurologic signs in central nervous system [CNS] lymphoma). The typical clinical signs and physical examination findings in cats and dogs with extranodal lymphomas are summarized in Table 80-2. Common extranodal forms in dogs include cutaneous and ocular lymphomas; in cats they include nasopharyngeal, ocular, renal, and neural lymphomas.

Cutaneous lymphoma is one of the most common extranodal forms of lymphoma in dogs; it is the most common extranodal lymphoma in dogs at our clinic, but it is rare in cats. The clinical signs and characteristics of the lesions are extremely variable, and they can mimic any primary or



TABLE 80-2

Clinical Signs and Physical Examination Findings in Dogs and Cats with Extranodal Lymphomas

ORGAN INVOLVED	CLINICAL PRESENTATION	PHYSICAL FINDING(S)
CNS	Solitary or multifocal CNS signs	Any neurologic finding
Eye	Blindness, infiltrates, photophobia	Infiltrates, uveitis, RD, glaucoma
Kidney	PU/PD, azotemia, erythrocytosis*	Renomegaly, renal masses
Lung	Coughing, dyspnea	None, radiographic changes
Skin	Any primary or secondary lesion	Any primary or secondary lesion

CNS, Central nervous system; RD, retinal detachment; PU/PD, polyuria/polydipsia.

<sup>\*</sup>Only in dogs.



PIG 80-1
Diffuse desquamative dermatopathy in a 13-year-old female spayed dog with mycosis fungoides (a specific type of epidermotropic cutaneous T-cell lymphoma). Clinical signs and lesions were present for almost 2 years.



FIG 80-2 Typical doughnut-shaped lesion in a Rottweiler with cutaneous T-cell lymphoma.

secondary skin lesion. Dogs with mycosis fungoides (an epidermotropic T-cell lymphoma) are usually first evaluated because of chronic alopecia, desquamation, pruritus, and erythema, eventually leading to plaque and tumor formation (Fig. 80-1). Mucocutaneous and mucosal lesions are relatively common, but generalized lymph node involvement may not be seen initially. A characteristic lesion in dogs with this form of lymphoma is a circular, raised, erythematous, donut-shaped, dermoepidermal mass that contains normal skin in the center (Fig. 80-2). Most of the cats with cutaneous lymphoma reported in the literature have been negative for FeLV viremia.

Ocular lymphoma occurs in both dogs and cats. Ocular involvement in dogs is commonly associated with the multicentric form, whereas both primary ocular involvement and ocular involvement associated with the multicentric form are common in cats. A variety of signs and lesions may be present in these animals, including photophobia, blepharospasm, epiphora, hyphema, hypopyon, ocular masses, third eyelid infiltration, anterior uveitis, chorioretinal involvement, and retinal detachment.

Nasopharyngeal lymphoma is relatively common in cats but is extremely rare in dogs. Clinical signs are similar to those seen in cats with any upper respiratory tract disorder and include sneezing, unilateral or bilateral nasal discharge (ranging from mucopurulent to frankly hemorrhagic), stertorous breathing, exophthalmos, and facial deformity; this is one of the most common forms of presentation of extranodal lymphoma seen in cats at our clinic.

Renal lymphoma is relatively common in cats but rare in dogs. Cats with this anatomic form are first evaluated because of vague clinical signs, usually secondary to chronic renal failure. On physical examination the cat is emaciated and usually anemic and has large, irregular, and firm kidneys; both kidneys are commonly affected. There is a purported association between renal and CNS lymphoma in cats, so some oncologists recommend using antineoplastic drugs that achieve high CNS concentrations (i.e., cytosine arabinoside, lomustine) in the treatment of cats with renal involvement in an attempt to prevent secondary CNS dissemination. This association has not been recognized at our clinic.

Cats and dogs with neural lymphoma are evaluated because of a variety of neurologic signs that reflect the location and extent of the neoplasms. Although CNS signs are most common, peripheral nerve involvement may occur occasionally in cats. Three forms of presentation are clinically recognized: solitary epidural lymphoma, neuropil (intracranial or intraspinal) lymphoma (also called true CNS lymphoma), and peripheral nerve lymphoma. The solitary epidural lymphoma is common in young FeLV-positive cats. Neural lymphomas can be primary (e.g., epidural lymphoma), or they may be secondary to the multicentric form; as discussed earlier, secondary CNS lymphoma may ocur in cats with the renal form. A relatively common presentation is that of a CNS relapse in dogs that have been receiving chemotherapy for multicentric lymphoma for months to years; these patients develop acute onset of neurologic signs, typically while the multicentric neoplasm is still in remission. This late CNS relapse is likely related to the fact that most drugs used to treat lymphoma do not cross the bloodbrain barrier when used at standard doses; thus the CNS becomes a sanctuary for tumor cells.

A variety of differential diagnoses should be considered in a cat or dog with suspected lymphoma. The clinician should always bear in mind that lymphomas are great imitators; they can mimic numerous different neoplastic and nonneoplastic disorders. The differential diagnoses in cats and dogs with lymphoma are similar to those in patients with leukemia (see Chapter 81).

Occasionally, dogs with lymphoma are evaluated because of clinical signs secondary to a paraneoplastic syndrome (i.e., molecularly mediated distant effects of the neoplasm). Paraneoplastic syndromes that have been encountered in dogs with lymphoma include hypercalcemia, monoclonal and polyclonal gammopathies, immune cytopenias, polyneuropathy, and hypoglycemia. Only hypercalcemia and gammopathies have been documented in cats with this neoplasm, although they are considerably less frequent than in dogs. Of all these syndromes, only humoral hypercalcemia of malignancy in dogs is of clinical relevance.

Hematologic and serum biochemical features. A variety of nonspecific hematologic and serum biochemical abnormalities can be detected in cats and dogs with lymphoma. The hematologic abnormalities result from the infiltration of bone marrow with neoplastic cells, splenic hypofunction or hyperfunction (caused by neoplastic infiltrates), chronic disease, or paraneoplastic immune-mediated abnormalities (i.e., immune hemolytic anemia or thrombocytopenia, both of which are extremely rare). Certain hematologicabnormalities (i.e., monocytosis, leukemoid reactions) may result from the local or systemic production of bioactive substances by the tumor cells (e.g., hematopoietic growth factors, interleukins). The serum biochemical abnormalities result either from the production of bioactive substances by the tumor cells (i.e., paraneoplasia) or from organ failure secondary to neoplastic infiltration. In general, the complete blood count (CBC) and biochemical profile are not diagnostic in cats and dogs with lymphoma.

Common hematologic abnormalities include nonregenerative anemia, leukocytosis, neutrophilia (with or without a left shift), monocytosis, abnormal lymphoid cells in peripheral blood (i.e., lymphosarcoma cell leukemia), thrombocytopenia, isolated or combined cytopenias, and leukoerythroblastic reactions, among others. Lymphocytosis is rare in dogs and cats with lymphoma; when present, it is usually of low magnitude (i.e., <10,000 to 12,000/µl).

Serum biochemical abnormalities are more common in dogs than in cats with lymphoma and consist mainly of hypercalcemia and gammopathies. Hypercalcemia is one of the most common paraneoplastic abnormalities in dogs with lymphoma, occurring in approximately 20% to 40% of the patients; it is extremely rare in cats, and it is more prevalent in dogs with mediastinal lymphoma than in those with the multicentric, alimentary, or extranodal forms. In most dogs with lymphoma and hypercalcemia, the tumor is of T-cell origin.

There are numerous molecular mechanism underlying hypercalcemia in dogs with lymphoma, but in most cases hypercalcemia is thought to occur as a result of the production of a parathormone-like protein, called PTHrp (PTHrelated protein), by the neoplastic cells. Markedly increased serum concentrations of 1,25-vitamin D have been documented in human patients with lymphoma and hypercalcemia. We have recently recognized a similar condition in dogs with lymphoma and hypercalcemia (most of the dogs were Boxers with mediastinal T-cell lymphoma).

Hyperproteinemia is another paraneoplastic abnormality that rarely occurs in cats and dogs with lymphoma. It may be secondary to the production of a monoclonal protein by the lymphoma cells and can result in the development of hyperviscosity syndromes. Polyclonal gammopathies may also be present in cats and dogs with lymphoma.

Imaging. Radiographic abnormalities in cats and dogs with lymphoma vary with the different anatomic forms but in general are secondary to lymphadenopathy or organomegaly (i.e., hepatomegaly, splenomegaly, renomegaly); occasionally, the infiltration of other organs (e.g., lungs) may

lead to the appearance of additional radiographic abnor-

Radiographic changes in cats and dogs with multicentric lymphoma include sternal or tracheobronchial lymphadenopathy or both; interstitial, bronchoalveolar, or mixed pulmonary infiltrates; pleural effusion (rare); intraabdominal lymphadenopathy (e.g., mesenteric or iliac); hepatomegaly; splenomegaly; renomegaly; or intraabdominal masses. Rarely, lytic or proliferative bone lesions are identified on plain abdominal or thoracic radiographs.

In cats and dogs with mediastinal lymphoma, radiographic changes are usually limited to the finding of an anterior (or, more rarely, posterior) mediastinal mass, with or without pleural effusion. In cats and dogs with alimentary lymphoma, abnormalities are rarely detected on plain abdominal radiographs (<50%). When present, they vary in nature but include mainly hepatomegaly, splenomegaly, and midabdominal masses. Positive contrast-enhanced radiography of the upper gastrointestinal tract usually reveals abnormalities in most animals. In a series of dogs with alimentary lymphoma evaluated at our clinic, abnormalities were found in all dogs that underwent positive contrastenhanced radiography of the upper gastrointestinal tract and included mucosal irregularities, luminal filling defects, and irregular thickening of the wall, suggestive of infiltrative mural disease.

Ultrasonography constitutes an invaluable tool for evaluating cats or dogs with suspected or confirmed intraabdominal lymphoma. The technique is also helpful in the evaluation of mediastinal masses in both species (see Chapter 79). Changes in the echogenicity of parenchymal organs (i.e., liver, spleen, kidneys) detected by this technique usually reflect changes in organ texture secondary to neoplastic infiltration. In addition, enlarged lymphoid structures or organs can easily be identified using this technique. Several abnormalities are commonly detected ultrasonographically in cats and dogs with intraabdominal lymphoma; these include hepatomegaly, splenomegaly, changes in the echogenicity of liver or spleen (mixed echogenicity or multiple hypoechoic areas), intestinal thickening, lymphadenopathy (Fig. 80-3), splenic masses, and effusion. In a study of 11 cats with alimentary lymphoma evaluated ultrasonographically at our clinic, we found hypoechoic masses of the gastric or intestinal wall, focal or diffuse gastric wall thickening, a symmetrical thickening of the intestinal wall, loss of the normal layered appearance of the gastrointestinal wall, and abdominal lymphadenopathy (Grooters et al., 1994). Fine-needle aspiration (FNA) and needle biopsy can also be easily performed using this technique to guide the placement of the needle.

# **Diagnosis**

The clinical signs and physical examination findings described in preceding paragraphs are usually suggestive of lymphoma. However, before instituting therapy, the clinician must confirm the diagnosis cytologically, histopathologically, or molecularly. In addition, a minimum database con-

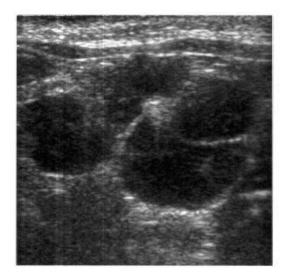


FIG 80-3 Mesenteric lymphadenopathy in a 12-year-old cat with diarrhea associated with an intestinal small cell lymphoma. Note the marked enlargement of the affected lymph node  $(3 \times 5 \text{ cm})$ .

sisting of a CBC, serum biochemistry profile, and urinalysis should be obtained if the owners are contemplating treatment.

In most cats and dogs with multicentric, superficial extranodal, mediastinal, or alimentary lymphoma, a diagnosis can easily be obtained by FNA cytologic studies of the affected organs or lymph nodes. The techniques for FNA and the cytologic features of lymphoma are described in detail in Chapter 75.

In our practice lymphomas can be diagnosed cytologically in approximately 90% of dogs and 70% to 75% of cats evaluated (i.e., usually in only 10% of the dogs and 25% to 30% of the cats is it necessary to perform a histopathologic, flow cytoemetric, or molecular evaluation of a lymph node or mass to establish a diagnosis). Until there is conclusive evidence that the histopathologic classification of canine and feline lymphomas offers prognostic information, the surgical removal of a lymph node or extranodal mass for histopathologic evaluation in an animal with a cytologic diagnosis of lymphoma is not necessarily indicated. A diagnosis based on cytologic findings rather than histopathologic findings yielded by an excisional lymph node biopsy also offers two major benefits: (1) It is associated with minimal or no morbidity, and (2) it is financially acceptable to most owners (i.e., approximate cost of a lymph node aspirate is \$70 to \$100; the cost for biopsy and histopathologic evaluation is \$300 to \$400).

New diagnostic methodologies commonly used in patients with lymphoma in our clinic include immunophenotyping by flow cytometry and clonal analysis by polymerase chain reaction (PCR). In the former, a sample of the affected organ/tissue is obtained by FNA and placed in an appropriate transport media. In the laboratory these cells are incubated with specific antibodies that recognize epitopes specific



# **TABLE 80-3**

TNM Staging System for Dogs and Cats with Lymphoma

CLINICAL FEATURES		
Solitary lymph node involvement		
More than one lymph node enlarged but on one side of the diaphragm (i.e., cranial or caudal)		
Generalized lymph node involvement		
Stage III findings, plus hepatomegaly and/or splenomegaly		
Any of the above, plus bone marrow or extranodal involvement substage a: asymptomatic substage b: sick		

TNM, Tumor, node, metastasis.

for T- or B-cells. Flow cytometric evaluation of the sample allows to immunophenotype the cell population. Clonal analysis by PCR also requires an FNA or a small biopsy specimen. Specific laboratories will evaluate the population of cells in question by PCR to determine if they are B- or T-cell in origin and if they are monoclonal or poyclonal. This technique has high sensitivity and specificity for distinguishing reactive lymphadenopathy from lymphoma (Lana et al., 2006).

After a diagnosis of lymphoma is confirmed, it is customary to stage the disease to obtain a prognosis. A staging system devised by the World Health Organization has been used for the past two decades for the staging of cats and dogs with lymphoma (Table 80-3). In this system, derived from the TNM (tumor, node, metastasis) staging system for neoplasms in humans, clinical and clinicopathologic information from the patient is used in an attempt to determine the extent of disease and correlate it with the prognosis. Unfortunately, it cannot be used prognostically (i.e., animals with stage I disease have survival times similar to those of animals with stage IV disease). The only prognostic information of clinical relevance in this system is the fact that asymptomatic (i.e., substage a) dogs with lymphoma have better prognosis than "sick" (i.e., substage b) dogs. A staging system that takes into account tumor bulk and FeLV status in cats with lymphoma provides some prognostic information when cats are treated with a specific chemotherapy protocol (Mooney et al., 1989). Until a new system is devised, it is advisable to determine the prognosis on the basis of the patient's overall clinical condition, the FeLV status (in cats), and any constitutional signs or severe hematologic and biochemical abnormalities the patient may have. Another important issue is that even though a specific staging protocol may be of some prognostic value in patients treated with a given chemotherapy protocol, it may not be so when a different drug combination is used. Moreover, at this time the effectiveness of more aggressive protocols in dogs and cats with advancedstage lymphoma is unknown.

At least a CBC, a serum biochemistry profile, and a urinalysis should be performed in all cats and dogs with lymphoma whose owners are contemplating therapy. In addition, FeLV and FIV tests should be performed in cats. The resulting minimum database can provide a wealth of information that can help the owner (and the clinician) decide whether to treat the patient. In addition, once a decision to treat the pet has been made, the nature of any clinicopathologic abnormalities usually dictates the treatment or treatments used. For example, in a dog with pronounced cytopenias caused by lymphomatous infiltration of the bone marrow, a highly myelosuppressive chemotherapy combination almost certainly will result in severe neutropenia and sepsis; it should therefore be avoided.

In cats and dogs with suspected CNS lymphoma, it is advisable to perform cerebrospinal fluid (CSF) analysis and advanced imaging (i.e., computed tomography [CT] scan or magnetic resonance imaging [MRI]). The finding of high numbers of neoplastic lymphoid cells and an increased protein concentration in a CSF sample is diagnostic for lymphoma. Because of their poor accessibility, the diagnosis of extradural masses usually requires the collection of a surgical specimen for cytologic or histopathologic evaluation.

As previously discussed, immunophenotyping of canine and feline lymphoma has become routine for most oncologists. This can be done by immunocytochemistry, immunohistochemistry, flow cytometry, or PCR for clonality. Published reports suggest that dogs with T-cell lymphoma treated with standard combination chemotherapy have a worse prognosis for remission and survival than dogs with B-cell tumors; however, in our experience, this is not the case. In a recent study we demonstrated that T-cell phenotype was not a negative prognostic factor in dogs with lymphoma treated with COP- or CHOP-based protocols (Hosoya et al., 2007). This is likely because most dogs with T-cell lymphoma received lomustine (CCNU), a drug that in our experience is effective in patients with T-cell phenotype.

#### Treatment

Once a diagnosis of lymphoma is established, the prognosis and potential therapeutic options should be discussed with the pet's owner. Remission rates in cats and dogs with lymphoma treated with various chemotherapy protocols are approximately 65% to 75% and 80% to 90%, respectively. Most cats with lymphoma treated with multiple-agent chemotherapy protocols are expected to live 6 to 9 months; approximately 20% of the cats live more than 1 year. Most dogs with lymphoma treated in a similar fashion are expected to live 12 to 16 months; approximately 20% to 30% of the dogs are alive 2 years after diagnosis. The approximate survival time in untreated cats and dogs with lymphoma is 4 to 8 weeks. Probably the most important reason for the shorter survival times in cats than in dogs with lymphoma is that remissions appear to be difficult to reinduce once the tumor has relapsed. In addition, the retrovirus-associated nonlymphomatous disorders that affect cats with lymphoma lead to shortened survival times (i.e., FeLV infection is a negative prognostic factor in cats with lymphoma).

In my experience, even if an animal has stage I nodal or extranodal lymphoma at the time of presentation, systemic dissemination of the disease usually occurs within weeks to months of diagnosis. However, occasionally solitary oral or cutaneous lymphomas may behave as true stage I diseases (i.e., there is no systemic dissemination). Therefore the mainstay of treatment for animals with lymphoma is chemotherapy, given the fact that lymphomas are (or will become) systemic neoplasms. Surgery, radiotherapy, or both can be used to treat localized lymphomas before or during chemotherapy. Half-body irradiation or chemotherapy and bone marrow transplantation have also been recently used to treat dogs with lymphoma (see Suggested Readings). General guidelines for the management of patients with lymphoma are presented here. The protocols recommended in this chapter have been used at our clinic with a success rate comparable to those of other treatments published in the literature.

There are two main chemotherapeutic approaches in dogs and cats with lymphoma: induction chemotherapy, followed by maintenance (and reinduction) or more aggressive chemotherapy for a finite period of time, at the end of which no maintenance chemotherapy is used. The former is usually done with a less aggressive COP (cyclophosphamide, vincristine, and prednisone)-based protocol, whereas the latter is usually based on CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-type protocols. An example of the latter is one of several University of Wisconsin (UW) protocols. CHOP-based protocols are similar to those used in people with high-grade lymphomas.

# **COP-Based Protocols**

When using COP-based protocols, the treatment of cats and dogs with lymphoma is divided into several phases, or strategies: induction of remission, intensification, maintenance, and reinduction of remission or "rescue" (Box 80-1). Immediately after diagnosis, a relatively nonaggressive multipleagent COP-based chemotherapy protocol is used to induce remission; in our clinic we frequently use the COAP protocol, with the addition of cytosine arabinoside to the COP protocol. During this phase, which lasts 6 to 8 weeks, patients are evaluated weekly by a veterinarian, at which time they receive an intravenous (IV) injection of an antimitotic agent (vincristine) in addition to undergoing a routine physical examination (with or without a CBC). If at the end of this phase the patient is considered to be in complete remission (CR; i.e., all neoplastic masses have completely disappeared), the maintenance phase is initiated. During this phase, a multipleagent chemotherapy protocol consisting of three drugs (chlorambucil [Leukeran], methotrexate, prednisone [LMP]) administered orally is used, so that the patient requires less intensive monitoring (once every 6 to 8 weeks). In my experience, maintenance chemotherapy is necessary when using COP-based protocols. Over the past few years, we have instructed the owners of pets with multicentric lymphoma

Chemotherapy Protocols Used to Treat Dogs and Cats\* with Lymphoma at the Ohio State University Veterinary Teaching Hospital

#### 1. Induction of Remission

#### a. COAP protocol†

Cyclophosphamide: 50 mg/m<sup>2</sup> PO q48h in dogs or 200-300 mg/m<sup>2</sup> PO q3 weeks in cats

Vincristine: 0.5 mg/m<sup>2</sup> IV weekly

Cytosine arabinoside: 100 mg/m² daily as an IV drip or SC for only 2 days in cats and 4 days in dogs

Prednisone: 50 mg/m<sup>2</sup> PO q24h for 1 week, then 20 mg/m<sup>2</sup> PO q48h

# b. COP protocol

Cyclophosphamide (Cytoxan®): 50 mg/m² BSA, PO, q48h; or 300 mg/m² BSA, PO, every 3 weeks (dogs or cats) Vincristine (Oncovin®): 0.5 mg/m² BSA, IV, once a week Prednisone: 40-50 mg/m² BSA, PO, q24h for a week; then 20-25 mg/m<sup>2</sup> BSA, PO, every other day.

#### c. UW-19 protocol (This protocol uses no maintenance chemotherapy-for additional information see text)

Week 1: Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV Asparaginase 400 IU/KG IM or SC Prednisone 2 mg/kg PO q24h

Cyclophosphamide 200-250 mg/m², IV Prednisone 1.5 mg/kg PO q24h Week 2:

Week 3: Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV Prednisone 1 mg/kg PO q24h

Doxorubicin 30 mg/m² (or 1 mg/kg if <10 kg) IV Week 4: Prednisone 0.5 mg/kg PO q24h

Week 5: No treatment

Week 6: Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV

Week 7: Cyclophosphamide 200-250 mg/m<sup>2</sup>, IV

Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV Week 8:

Week 9: Doxorubicin 30 mg/m² (or 1 mg/kg if <10 kg) IV

Week 10: No treatment

Week 11: Vincristine 0.5-0.75 mg/m², IV Week 12: Cyclophosphamide 200-250 mg/m², IV

Week 13: Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV

Week 14: Doxorubicin 30 mg/m² (or 1 mg/kg if <10 kg) IV

Week 15: No treatment

Week 16: Vincristine 0.5-0.75 mg/m<sup>2</sup>, IV

Week 17: Cyclophosphamide 200-250 mg/m², IV Week 18: Vincristine 0.5-0.75 mg/m², IV

Week 19: Doxorubicin 30 mg/m<sup>2</sup> (or 1 mg/kg if <10 kg) IV

# 2. Intensification

# Dogs

L-Asparaginase (Elspar): 10,000-20,000 IU/m<sup>2</sup> IM (one or two doses

Vincristine (Oncovin): 0.5-0.75 mg/m<sup>2</sup> IV q1-2 weeks

#### Cats

Doxorubicin (Adriamycin): 1 mg/kg IV q3 weeks

Mitoxantrone (Novantrone): 4-6 mg/m<sup>2</sup> IV q3 weeks

# 3. Maintenance1

a. LMP protocol

Chlorambucil:  $20 \text{ mg/m}^2 \text{ PO q2}$  weeks Methotrexate:  $2.5 \text{ mg/m}^2 \text{ PO two}$  or three times per week

Prednisone: 20 mg/m<sup>2</sup> PO q48h

#### b. COAP protocol

Use as above every other week for six treatments, then every third week for six additional treatments, then try to maintain the animal on one treatment every fourth week. Maintenance therapy is continued until the tumor relapses.

#### 4. Rescue

#### Dogs

a. D-MAC protocol (14-day cycle)

Dexamethasone: 0.5 mg/lb (0.23 mg/kg) PO or SC on days 1 and 8

Actinomycin D: 0.75 mg/m² as IV push on day 1

Cytosine arabinoside: 200-300 mg/m² as IV drip over 4 hours or SC on day 1

Melphalan: 20 mg/m² PO on day 8§

b. AC protocol (21-day cycle)

Doxorubicin (Adriamycin): 30 mg/m² (or 1 mg/kg for dogs under 10 kg) IV on day 1

Cyclophosphamide (Cytoxan): 100-150 mg/m<sup>2</sup> PO on days 15 and 16

c. CHOP protocol (21-day cycle)

Cyclophosphamide (Cytoxan): 200-300 mg/m² PO on day 10 Doxorubicin (Adriamycin): 30 mg/m² (or 1 mg/kg for dogs under 10 kg) IV on day 1

Vincristine (Oncovin): 0.75 mg/m² IV on days 8 and 15 Prednisone: 20-25 mg/m<sup>2</sup> PO q48h

#### Cats

a. AC protocol (21-day cycle)

Doxorubicin (Adriamycin): 1 mg/kg IV on day 1

Cyclophosphamide (Cytoxan): 200-300 mg/m² PO on day 10 or 11

Dexamethasone (4 mg/cat q1-2 weeks can be added to this protocol)

b. MiC protocol (21-day cycle)

Mitoxantrone (Novantrone): 4-6 mg/m² as IV drip over 4-6 hours on day 1

Cyclophosphamide (Cytoxan): 200-300 mg/m² PO on day 10 or 11

Dexamethasone (4 mg/cat q1-2 weeks can be added to this protocol)

c. MiCA protocol (21-day cycle)

Mitoxantrone (Novantrone): 4-6 mg/m<sup>2</sup> in IV drip over 4-6 hours on day 1

Cyclophosphamide (Cytoxan): 200-300 mg/m<sup>2</sup> PO on day 10 or 11

Cytosine arabinoside (Cytosar-U): 200 mg/m<sup>2</sup> in IV drip over 4-6 hours (mixed in the same bag with mitoxantrone) on day 1

Dexamethasone (4 mg/cat a 1-2 wks can be added to this protocol)

#### 5. "Low-Budget" Protocols

Prednisone: 50 mg/m<sup>2</sup> PO q24h for 1 week; then 25 mg/m<sup>2</sup> PO q48h

Chlorambucil: 20 mg/m² PO q2 weeks

Lomustine (CCNU; Ceenu): 60 mg/m<sup>2</sup> PO q3 weeks in dogs; 10 mg (total dose) q3 weeks in cats

Prednisone and chlorambucil: doses as above Prednisone and lomustine: doses as above

PO, By mouth; IV, intravenous; SC, subcutaneous; BSA, body surface area; IM, intramuscular.

\* Unless otherwise specified, protocols can be used in both dogs and cats.

† Use for 6-10 weeks, then use LMP.

‡Use until relapse occurs, then go to "rescue." § After four doses, substitute Leukeran (20 mg/m² PO q2 weeks) for Alkeran.

The duration of chemotherapy using this protocol is variable.

to closely monitor the size of the lymph nodes in their pets; when the nodes start enlarging (i.e., relapse), we add a fourth drug to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m<sup>2</sup>, IV, q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months.

The maintenance or modified maintenance phase continues until the tumor relapses (i.e., is out of remission), at which time the reinduction phase begins. This phase is similar to the induction phase in that intensive treatments are used. Once remission is obtained, the patient is started again on a modified maintenance protocol. If at the end of the induction phase the patient is not in CR, we recommend that intensification with L-asparaginase be done before the maintenance phase is initiated. In addition to the chemotherapeutic approach discussed in this section, a variety of protocols have been used successfully in the treatment of cats and dogs with lymphoma. (See Suggested Readings for additional information.)

Induction of remission. As previously discussed, my protocol of choice for the induction of remission is COAP. The agents in this protocol consist of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone; these four drugs are currently available as generic products. The dosages are specified in Box 80-1. These drugs belong to four different categories, have different mechanisms of action, and do not have superimposed toxicities (with the exception of cyclophosphamide and cytosine arabinoside, both of which are myelosuppressive; however, the latter is used only for a short period); thus they fulfill the basic criteria of multipleagent chemotherapy described in Chapter 77. The cytosine arabinoside is usually administered by the subcutaneous (SC) route because, given its short half-life and S-phasespecific mechanism of action, an IV bolus injection results in minimal cell kill; SC administration of this drug is painful in cats (and in some dogs). IV infusion of the agent is also associated with myelosuppression. The induction phase lasts 6 to 8 weeks, and weekly visits to the veterinarian are necessary during this time.

During the induction phase toxicity is minimal (<15%) and client compliance is high because most of the toxic signs are hematologic (i.e., cytopenias) and usually do not result in clinical signs that can be detected by the owners. The dose-limiting toxicity of this induction protocol is hematologic (i.e., myelosuppression leading to neutropenia); the neutrophil nadir usually occurs around day 7 or 8 because two myelosuppressive agents (i.e., cyclophosphamide and cytosine arabinoside) are given during the initial 2 to 4 days of treatment. In most cases the neutropenia is mild (2000 to 3500 cells/μl). The neutropenia is severe if the animals have neoplastic bone marrow infiltration before the initiation of treatment, have FeLV- or FIV-associated myelodysplasia or other retrovirus-associated bone marrow disorders, or receive the cytosine arabinoside by constant-rate IV infusion rather than by the SC route. Also, anecdotally, neutropenia appears to be common in Cocker Spaniels receiving this protocol. Dosage adjustments in cats and dogs that develop neutropenia are described in Chapter 78. Gastrointestinal toxicity is minimal to nonexistent; however, cats receiving cyclophosphamide occasionally become anorectic. Consequently, this drug should be administered once every 3 weeks in cats (as opposed to every other day in dogs; see Box 80-1). If anorexia develops, treatment with cyproheptadine (Periactin; Merck Sharp & Dohme, West Point, Pa.), an antiserotonin compound, at a dosage of 1 to 2 mg per cat PO q8-12 hours is indicated. Hair loss is also minimal, and it occurs primarily in woolly-haired dogs (e.g., Poodle, Bichon Frise); cats (and some dogs) may shed their tactile hairs during treatment.

During this phase, owners are instructed to monitor their pet's appetite and activity level, measure their lymph nodes (if superficial lymphadenopathy was present initially), and take their pet's rectal temperature daily (pyrexia is usually secondary to neutropenia and bacteremia or sepsis). If pyrexia develops, owners are instructed to contact their veterinarian immediately so that their pet can undergo a complete physical examination and CBC (for additional information, see Chapter 78). Treatment with COAP results in CR within 1 to 14 days of the start of therapy in most animals (>85% in dogs, >70% in cats). This remission is usually maintained throughout the induction phase.

In dogs with diffuse alimentary lymphoma we use a more aggressive doxorubicin-containing protocol (CHOP; see Box 80-1) because, in my experience, the response rate to COAP is low. This protocol is more expensive and more likely to cause adverse effects than the COAP protocol. We typically use lomustine (CCNU) in dogs with epidermotropic T-cell lymphoma (see Box 80-1).

In dogs and cats with multicentric (or any other anatomic form of) lymphoma coexisting with neurologic signs, we usually use the COAP protocol but administer the cytosine arabinoside as a continuous IV infusion (200-400 mg/m<sup>2</sup> as an IV infusion over 24 hours for 1 to 4 days) in order to attain high concentrations of this drug in the CNS. This protocol tends to cause marked myelosuppression in cats, so we typically administer cytosine arabinoside as a 12- to 24-hour infusion (200 mg/m<sup>2</sup>) in this species. More information on the treatment of dogs and cats with suspected or confirmed CNS lymphoma is given later in this chapter.

Maintenance. The protocol recommended for the maintenance phase of treatment is LMP ("lump"), which consists of chlorambucil, methotrexate, and prednisone (see Box 80-1). These three drugs also act by three different mechanisms of action and have different toxicities. The advantages of this protocol include its reduced cost compared with the cost of the induction phase; its ease of administration (all the drugs are administered orally by the owners); its minimal toxicity; and the fact that intensive monitoring by a veterinarian is not necessary.

The toxicities associated with LMP maintenance chemotherapy are minimal. Of the three drugs in this protocol, methotrexate is the only one that is associated with moderate to severe toxicity. In approximately 25% of dogs and cats receiving methotrexate, gastrointestinal tract signs consisting of anorexia, vomiting, or diarrhea develop. Anorexia and vomiting are more common than diarrhea and usually occur after the patient has been receiving the drug for more than 2 weeks. In these cases treatment with an antiemetic, such as metoclopramide, on the days the animal receives the methotrexate, at a dosage of 0.1 to 0.3 mg/kg PO every 8 hours, alleviates or eliminates the upper gastrointestinal tract signs. We have recently used maropitant (Cerenia, Pfizer Animal Health, Kalamazoo, Mich.) at a dosage of 2 mg/kg PO every 24 hours to prevent chemotherapy-associated nausea and vomiting. Gastroprotectants, such as famotidine (0.5 mg/kg PO q24h) may also be effective in preventing or minimizing this adverse effect. In cases of methotrexate-associated diarrhea, treatment with a bismuth subsalicylate-containing product (Pepto-Bismol) may also alleviate or eliminate the signs; however, it may be necessary to discontinue the drug. Hematologic toxicity associated with LMP therapy is minimal to nonexistent. In a very small proportion of cats (i.e., <5%) receiving chlorambucil for weeks to months, serum biochemical abnormalities consistent with cholestasis that resolve on discontinuation of the drug may develop. Recently, tonic or tonic-clonic convulsions have been decribed in cats receiving chlorambucil.

During this phase the patient is examined every 6 to 8 weeks, at which time a complete physical examination and a CBC are performed. As with the induction protocols, owners are instructed to monitor their pet's activity, appetite, behavior, rectal temperature, and lymph node size. As previously discussed, over the past few years we have been instructing the owners of pets with multicentric lymphoma to closely monitor the size of the lymph nodes in their pets; when the nodes start enlarging (i.e., relapse), a fourth drug is added to the LMP protocol (usually vincristine, at a dosage of 0.5-0.75 mg/m², IV, q1-2 weeks). This usually suffices to reinduce remission and maintain it for several weeks or months.

Most animals treated with this protocol remain in remission for approximately 3 to 6 months. If a relapse occurs, reinduction of remission (as discussed next) is instituted. After remission is reinduced, animals can be treated with a modified maintenance protocol, as described in previous paragraphs.

Reinduction of remission or rescue. Virtually every dog and cat with lymphoma treated with induction followed by maintenance chemotherapy eventually relapses; this generally occurs 3 to 6 months after the start of induction therapy (median: approximately 4 months), but it can occur within weeks of starting the maintenance phase or years after the original diagnosis was made. At this time, reinduction of remission is indicated. In my experience, remission can be reinduced one to four additional times in most dogs with relapsing lymphoma. Reinduction of remission is usually not as successful in cats as in dogs (i.e., remission cannot be reinduced in most cats with relapsing lymphoma). Therefore the following discussion on "rescue" pertains mostly to dogs with lymphoma.

There are numerous "rescue" protocols described in the literature, and as a general rule, the practitioner may have difficulty deciding what protocol to choose. We currently use

the D-MAC protocol (see Box 80-1), which consists of dexamethasone, melphalan (Alkeran; Burroughs Wellcome, Research Triangle Park, N.C.), cytosine arabinoside (Cytosar-U), and actinomycin D (Cosmegen; Merck Sharp & Dohme, West Point, Pa.) as our trump card for rescue (Alvarez et al., 2006). This protocol results in an over 70% remission rate in dogs with relapsing lymphoma; it has a relatively low toxicity compared with that of doxorubicin-containing protocols, and it is necessary for the owner to go the veterinarian only once every 2 weeks (instead of every week). The median duration of remission using the D-MAC protocol was 61 days (range 2 to 467+ days). Previous use of doxorubicin and failure to induce remission with the induction protocol were negative prognostic factors for response to this protocol. Thrombocytopenia occurred in 56% of the dogs, neutropenia in 17%, and gastrointestinal toxicity in 22%; three of the 56 dogs required hospitalization because of toxicity. Because the long-term use of melphalan is associated with severe chronic thrombocytopenia, chlorambucil (Leukeran), 20 mg/m<sup>2</sup>, is substituted for melphalan after four cycles. If complete or partial remissions are achieved after the administration of four to six cycles of D-MAC, the patient can be started on a maintenance protocol again.

If the response to D-MAC is poor (i.e., the disease progresses), the CHOP protocol is recommended (see Box 80-1). Our protocol calls for two or three cycles of CHOP once the tumor has relapsed; if CR is obtained, the patient is started on maintenance chemotherapy at the end of the second or third CHOP cycle. The maintenance protocol in these animals also includes LMP, with the possible addition of vincristine (0.5 to 0.75 mg/m² IV once weekly to every other week, alternating weeks with the chlorambucil) or cytosine arabinoside (200 to 400 mg/m² subcutaneously every other week, alternating weeks with the chlorambucil).

After a second relapse occurs, D-MAC or CHOP is administered for two additional cycles, as described in the preceding paragraph. In our experience, after the second and third relapses, the percentage of animals in which remission can be easily reinduced decreases with each subsequent cycle. This likely stems from the development of multiple-drug resistance by the tumor cells. Other protocols that have been successful in reinducing remission in dogs with lymphoma are listed in Box 80-1. Although the probability of reinducing remission is considerably lower in cats than in dogs, one of the protocols listed in Box 80-1 can be used for this purpose.

In cats doxorubicin- or mitoxantrone-containing protocols have been used with some degree of success (see Box 80-1); asparaginase-containing protocols may also be used but generally are not as effective as in dogs.

Intensification. If a dog is undergoing induction therapy but only partial remission (PR) is obtained, intensification with one or two doses of L-asparaginase (Elspar; 10,000 to 20,000 IU/m² IM, repeated once at a 2- to 3-week interval) may be indicated. This drug can rapidly induce CR in most dogs with lymphoma that have shown only PR while receiving COP-based protocols. Asparaginase should not be used

in dogs with a history of pancreatitis or in those that are at high risk for acute pancreatitis (i.e., obese, middle-age female dogs). In my experience, L-asparaginase appears to be less effective in cats than in dogs; doxorubicin (1 mg/kg IV q3 weeks) or mitoxantrone (4 to 6 mg/m² IV q3 weeks; Novantrone; Lederle, Wayne, N.J.) can be used as intensifying agents in cats. In a recent study only two of thirteen (15%) cats with lymphoma treated with L-asparaginase underwent CR, and two of thirteen (15%) underwent PR; these response rates are quite a bit lower than those reported in dogs (i.e., >70%) (LeBlanc et al., 2007).

#### **CHOP-Based Protocols**

Although I do not personally use CHOP-based protocols, such as the UW-19 or UW-25, to treat dogs with multicentric lymphoma, I occasionally use them in dogs with diffuse small intestinal lymphoma. However, numerous articles on CHOP-based protocols in dogs with lymphoma have appeared in the literature in the last two decades. The most attractive aspect of using CHOP-based protocols is that the patient is under treatment for a finite period of time (i.e., 19 weeks for the UW-19 and 25 weeks for the UW-25); when the protocol ends, the patient is closely monitored but does not receive additional chemotherapy (i.e., no maintenance). This feature is extremely important in humans undergoing chemotherapy, in whom the prevalence of adverse effects is extremely high and the patient is looking forward to a life without chemotherapy. However, people considering chemotherapy for their pets may not share this sentiment. As a general rule, the probability and severity of toxicity with CHOP-based protocols are higher than with COP-based protocols. Box 80-1 lists the UW-19 protocol, commonly used by numerous oncologists.

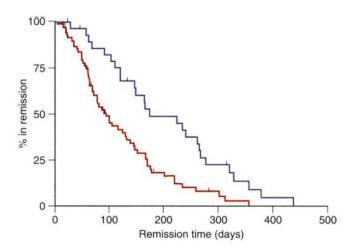
# Should You Use COP-Based or CHOP-Based Protocols?

Clinicians have been debating the relative merits of COPand CHOP-based protocols for several years. However, because most institutions or clinicians prefer one protocol over the other, because most of the reports on COP-based protocols are 10 to 20 years old, and because in most reports of COP- or CHOP-based chemotherapy studies the endpoint has been remission times, rather than survival times, a definitive answer is not readily available.

However, in our clinic we have a similar number of patients treated with COP- and CHOP-based (UW-19) protocols; these patients are cared for by the same group of clinicians and technicians. We recently published the results of a retrospective study of 101 dogs with multicentric lymphoma treated with either COP-based protocols with maintenance chemotherapy (n = 71) or CHOP-based protocol (UW-19, n = 30) in our clinic (Hosoya et al., 2007). The probability of achieving CR or PR was similar for both protocols (92% for dogs treated with COP versus 100% for dogs treated with CHOP). Although the median duration of remission was significantly longer in dogs treated with CHOP than in those treated with COP (174 versus 94 days),

the median survival times (MST) were not statistically different between groups (Figs. 80-4 and 80-5). The MST in dogs receiving COP was 309 days, compared with 275 days in dogs receiving the UW-19 protocol. The MST was similar for dogs with B- or T-cell lymphoma treated with the COP-based protocols (321 versus 378 days, respectively); there were not enough dogs with T-cell phenotype treated with the UW-19 to perform statistical analysis.

The prevalence of severe myelosuppression and adverse gastrointestinal effects was significantly higher in dogs receiving CHOP chemotherapy. The cost of treatment using both protocols was similar. Therefore there is no advantage of one protocol over the other one, and the clinician must



**FIG 80-4** Kaplan Meier curves for duration of first remission in dogs with multicentric lymphoma treated with COAP (red line) or CHOP (blue line). The median duration of remission was significantly longer in dogs treated with CHOP chemotherapy (p < 0.01). (From Hosoya et al., 2008.)

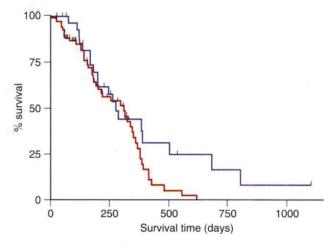


FIG 80-5
Kaplan Meier survival curves in dogs with multicentric lymphoma treated with COAP (red line) or CHOP (blue line). The median duration of remission was not significantly different between groups (p = 0.09). (From Hosoya et al., 2008.)

make a decision based on a variety of factors (e.g., the owner's perception, the patient's clinical signs and other concurrent illnesses, cost).

Management of solitary and extranodal lymphomas. The clinician faces a dilemma when confronted with a dog or cat with a solitary lymphoma, regardless of whether it is nodal (i.e., stage la disease) or extranodal (i.e., a solitary cutaneous or oral mass). Should the mass (or lymph node) be treated in the same manner as other solitary malignancies (i.e., by wide surgical excision)? Should the patient be treated primarily with chemotherapy? Should the patient be treated with a combination of surgery, irradiation, and chemotherapy? Unfortunately, there are no correct answers to these questions.

In my experience, seemingly solitary lymphomas become (or already are) systemic in most animals. Exceptions include some oral and some cutaneous solitary T-cell lymphomas. Although cures have been achieved through the surgical excision or irradiation of solitary lymphomas, they are extremely rare. Therefore it is important not to underestimate the malignant behavior of this neoplasm by treating the patient only with a local treatment modality, such as surgery or radiotherapy. The following guidelines can be used in this subset of patients:

- 1. If the tumor is easily resectable (e.g., cutaneous mass, superficial lymph node, intraocular mass) and the surgical procedure does not pose a considerable risk to the patient, the mass should be resected and the animal treated with chemotherapy.
- 2. If the mass is difficult or impossible to resect or if a major surgical procedure would pose an undue risk for the animal, an FNA or a needle biopsy specimen of the mass should be obtained and the animal treated with chemotherapy (with or without radiotherapy of the primary lesion).

Radiotherapy constitutes an excellent treatment modality for dogs and cats with solitary lymphomas because lymphoma cells are extremely radiosensitive. Marked responses (CR or PR) are seen within hours or days of the start of such treatment. Different sources and protocols have been used in cats and dogs with lymphoma, but in general 3 to 5 Gy (300 to 500 rad) per fraction is delivered daily or thrice weekly for a total of six to ten fractions (total dose, 30 to 50 Gy [3000 to 5000 rad]). We have successfully used coarse fractionation radiotherapy (7 Gy once a week for 4 treatments) followed by maintenance chemotherapy (discussed later) in dogs with solitary oral T-cell lymphomas. Special settings in which radiotherapy is beneficial include CNS lymphomas (see following paragraphs) and upper airway lymphomas that cause respiratory compromise.

Another decision the clinician must make if chemotherapy is to be used is which protocol to use and for how long. There are also no specific guidelines for this. We use a standard induction chemotherapy protocol (COAP) in most cats and dogs with solitary lymphoma after they have undergone

surgical excision or irradiation. After completion of the induction phase, the animals are treated with a maintenance protocol (LMP) and remission is reinduced as necessary (as in other forms of lymphoma). In our experience, early relapses occur in most animals treated with only maintenance chemotherapy protocols after the surgical excision of solitary lymphomas.

Central nervous system lymphoma. The treatment of choice for cats and dogs with primary or secondary epidural lymphoma is radiotherapy plus multiple-agent chemotherapy. If radiotherapy facilities are not available, multiple-agent chemotherapy is an effective alternative approach. It is my clinical impression that the surgical excision of such masses does not provide a significant advantage over chemotherapy alone or radiotherapy plus chemotherapy, given the fact that the latter two forms of treatment consistently induce rapid remissions (i.e., within 12 to 36 hours of the initiation of therapy). However, because surgery may be necessary to confirm the diagnosis, surgical excision of the mass is usually attempted at that time. If radiotherapy is available, three to five doses weekly of 3 to 4 Gy, to a total of 25 to 30 Gy, are indicated. The COAP protocol alone has been effective in inducing remission in cats with epidural lymphoma.

In cats and dogs with lymphoma of the neuropil (i.e., true CNS lymphoma), chemotherapy with or without radiotherapy is the preferred protocol. In animals in which it is possible to localize the lesion (i.e., by neurologic examination, CT, or MRI), radiotherapy should be used in conjunction with chemotherapy. If this is not possible, diffuse craniospinal irradiation can be performed.

Intrathecal chemotherapy can be used in cats and dogs with confirmed or highly likely neuropil lymphoma. The drug of choice is cytosine arabinoside (Cytosar-U) because it is almost nontoxic, it is inexpensive, and it is easy to administer. However, IV administration of this drug as a constant rate infusion (CRI) at dosages of 200 to 600 mg/m² over 24 to 72 hours achieves similar results and is our preferred approach. Responses to intrathecal or IV CRI cytosine arabinoside are usually quite spectacular. Dogs and cats that are tetraparetic, demented, or comatose usually regain normal neurologic status within 6 to 48 hours of receiving the first dose of this agent. In addition, disappearance of the neoplastic cells from the CSF can be documented within hours of the injection.

We frequently induce clinical and cytologic remission (i.e., normal neurologic status and disappearance of neoplastic cells from CSF) in cats and dogs with primary or secondary CNS lymphoma treated with COAP (using cytosine arabinoside as an IV infusion). As previously discussed, an alternative drug that crosses the blood-brain barrier and is effective in eliminating lymphoma cells is lomustine (CCNU; see Box 80-1) administered at a dosage of 60 mg/m² PO every 3 weeks in dogs and at a dosage of 10 mg/cat every 3 weeks in cats; we have seen marked improvement or disappearance of neurologic signs in dogs and cats with lymphoma treated with this drug.

Despite the fact that remissions are easily attained in dogs and cats with CNS lymphoma, they are relatively short in duration compared with the duration of remissions in dogs and cats with disease in other anatomic locations. Most dogs and cats with CNS lymphoma relapse within 2 to 4 months of diagnosis; however, prolonged remissions (i.e., 6 to 12 months) are possible.

Ocular lymphoma. Ocular lymphoma can be treated using a variety of modalities. However, the eye behaves similarly to the blood-brain barrier in that adequate intraocular concentrations of chemotherapeutic agents are usually difficult to attain. If the clinician and owner want to try to preserve the animal's eye, there are several alternatives to enucleation. As in animals with CNS lymphoma, the administration of cytosine arabinoside as a slow IV drip usually results in remission of the tumor. Lomustine is also effective in dogs and cats with intraocular lymphoma.

Cutaneous lymphoma. Cutaneous lymphoma is the most common extranodal form of lymphoma in dogs seen at the Veterinary Teaching Hospital of The Ohio State University. In dogs with cutaneous involvement secondary to multicentric lymphoma, we use a standard chemotherapy protocol (i.e., COAP). In dogs with epitheliotropic T-cell lymphomas we use either doxorubicin-containing (i.e., CHOP; see Box 80-1) or lomustine (CCNU)-containing protocols. In a recent study of 46 dogs with epidermotropic cutaneous T-cell lymphoma, 15 (33%) underwent CR and 23 (50%) underwent PR, for a response rate of 83% (Risbon et al., 2006). The median number of treatments to achieve a response was 1 (range, 1-6). The overall median duration of response was 94 days (range, 22-282). Sixteen dose reductions were required because of neutropenia (10/46), thrombocytopenia (1/46), anemia (1/46), increased liver enzyme activity (3/46), or unspecified reasons (1/46).

Alimentary lymphoma. We use standard chemotherapy protocols (i.e., COAP) in dogs and cats with solitary mural or nodal (e.g., mesenteric or ileocecocolic lymph node) involvement. Even though surgery is not necessarily indicated for these dogs and cats, a fair number are referred after exploratory surgery and an incisional or excisional biopsy has been performed. In general, the response in these animals is good. Dogs and cats with diffuse intestinal lymphoma usually respond poorly to chemotherapy. Responses to doxorubicin-containing protocols (i.e., CHOP) appear to be better than those to COAP, although survival times are short (4 to 6 months). Dogs with colorectal lymphoma and cats with gastric lymphoma tend to respond extremely well to COAP chemotherapy; we have documented remission times in excess of 3 years in these subsets of patients. In cats this may be related to the fact that Helicobacter spp. may play a role in the development of gastric lymphoma, as H. pilori does in people; we treat all cats with gastric lymphoma with combination chemotherapy and antibiotics proven effective in cats with Helicobacter infection.

In cats with epitheliotropic intestinal lymphoma, a common, small lymphocytic form of the disease in older individuals, we have used a very conservative approach with excellent results. We administer a combination of chlorambucil (20 mg/m<sup>2</sup>, PO q2 weeks) plus prednisone (1-2 mg/kg, PO q24-48h) or dexamethasone (4 mg/cat, PO q1-2 weeks); if clinical signs do not improve within 3 or 4 weeks, we add vincristine (0.5 mg/m<sup>2</sup>, IV, q1-2 weeks). Most cats treated with this protocol have marked improvement of the clinical signs and typically gain weight. Interestingly, some of the cats exhibit no appreciable decrease in mesenteric lymph node size, despite the remarkable clinical improvement. For these cats I use the approach of "treating the patient, not the disease" (i.e., as long as the patient feels well and is free of clinical signs, the current treatment is continued).

# "Low-Budget" Lymphoma Protocols

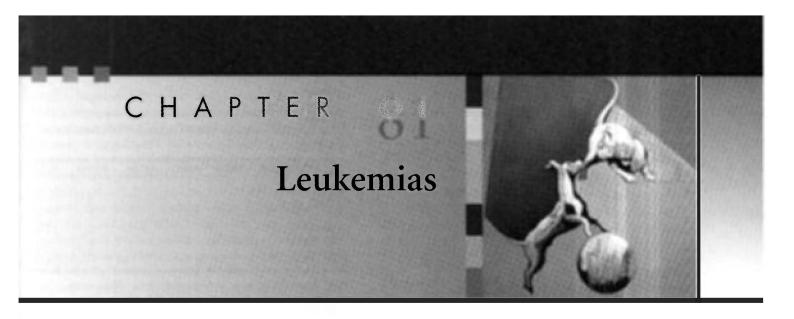
Quite frequently, the clinician is evaluating a dog or cat with lymphoma that should benefit from chemotherapy, but because of finances or other issues (e.g., time commitment) the owners are not interested in the standard multiagent chemotherapy approach. Because most of these patients are asymptomatic, they would benefit from some form of therapy. In our clinic we have used one of the following quite successfully: prednisone alone, prednisone and chlorambucil, chlorambucil alone, lomustine alone, or prednisone and lomustine. Although the duration of remission is shorter than when using COP-based protocols, most of these patients (and their owners) enjoy prolonged (i.e., months), good-quality survival times. These protocols are listed in Box 80-1.

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# CHAPTER OUTLINE

DEFINITIONS AND CLASSIFICATION LEUKEMIAS IN DOGS Acute Leukemias

Chronic Leukemias LEUKEMIAS IN CATS

Acute Leukemias Chronic Leukemias

# **DEFINITIONS AND CLASSIFICATION**

Leukemias are malignant neoplasms that originate from hematopoietic precursor cells in the bone marrow. Because these cells are unable to undergo terminal differentiation or apoptosis, they self-replicate as a clone of usually immature (and nonfunctional) cells. The neoplastic cells may or may not appear in peripheral circulation; thus the confusing terms *aleukemic* and *subleukemic* are used to refer to leukemias in which neoplastic cells proliferate within the bone marrow but are absent or scarce in the circulation.

Leukemias can be classified philogenetically into two broad categories according to the cell line they originate from: lymphoid and myeloid (or nonlymphoid; Table 81-1). The term myeloproliferative disease or disorder has also been used to refer to myeloid leukemias (mainly to the acute forms). On the basis of their clinical course and the cytologic features of the leukemic cell population, leukemias can also be classified as acute or chronic. Acute leukemias are characterized by an aggressive biologic behavior (i.e., death ensues shortly after diagnosis if the patient is not treated) and by the presence of immature (blast) cells in bone marrow or blood. Chronic leukemias have a protracted, often indolent course, and the predominant cell is a well-differentiated, late precursor (i.e., lymphocyte in chronic lymphocytic leukemia [CLL] and neutrophil in chronic myeloid leukemia [CML]). In dogs (and possibly in cats) CML can undergo blast transformation (blast crisis), during which the disease behaves like

an acute leukemia and is usually refractory to therapy. Blast crises do not appear to occur in dogs or cats with CLL.

Acute leukemias may be difficult to classify morphologically as myeloid or lymphoid on the basis of the evaluation of Giemsa- or Wright's-stained blood or bone marrow smears because poorly differentiated blasts look similar under the light microscope. In veterinary medicine cytochemical stains are used routinely in several diagnostic laboratories to establish whether the blasts are lymphoid or myeloid and also to subclassify myeloid leukemias, as described later (i.e., myeloid versus monocytic versus myelomonocytic). These cytochemical stains reveal the presence of different enzymes in the cytoplasm of the blasts, which aids in establishing their origin (Table 81-2).

Immunophenotyping of canine and feline leukemic cells using monoclonal antibodies is now available in teaching institutions and some commercial diagnostic laboratories; however, clinical correlations between immunophenotype and prognosis have not yet been established, although it appears that certain phenotypes may be associated with poor prognosis.

A classification scheme for acute leukemia in people was devised by a group of French, American, and British investigators (the FAB scheme) and was based on the morphologic features of the cells in Giemsa-stained smears of blood and bone marrow and the clinical presentation and biologic behavior of the disease. Because this scheme has not yet proved to be prognostically or therapeutically applicable to cats or dogs, it is not discussed here (see Suggested Readings for additional information on the FAB scheme in people and animals).

The terms *preleukemic syndrome* and *myelodysplastic syndrome* (MDS, or myelodysplasia) refer to a syndrome of hematopoietic dysfunction and specific cytomorphologic changes that precedes the development of acute myelogenous leukemia by months to years. The syndrome is characterized by cytopenias and a hypercellular bone marrow and appears to be more common in cats than in dogs. The clinical and hematologic features of cats and dogs with MDS are discussed at the end of this chapter.



TABLE 81-1

Classification of Leukemias in Dogs and Cats

CLASSIFICATION	SPECIES
Acute Leukemias Acute myeloid (myelogenous) leukemia (AML)	
Undifferentiated myeloid leukemia (AML-M <sub>o</sub> ) Acute myelocytic leukemia (AML-M <sub>1-2</sub> ) Acute progranulocytic leukemia (AML-M <sub>3</sub> )	D, C D, C
Acute myelomonocytic leukemia (AMML; AML- M <sub>4</sub> )	D, C
Acute monoblastic/monocytic leukemia (AMoL; AML-M <sub>5</sub> )	D, C
Acute erythroleukemia (AML-M <sub>6</sub> ) Acute megakaryoblastic leukemia (AML-M <sub>7</sub> )	C, D <b>?</b> D, C
Acute lymphoblastic leukemia (ALL)	
All-l <sub>1</sub> All-l <sub>2</sub> All-l <sub>3</sub> Acute leukemia of large granular lymphocytes {LGL}	D, C; D, C D, C
Subacute and Chronic Leukemias	
Chronic myeloid (myelocytic) leukemia (CML) Chronic myelomonocytic leukemia (CMML) Chronic lymphoid (lymphocytic) leukemia (CLL) Large granular lymphocyte (LGL) variant	D > C D D > C D

D, Dog; C, cat; ?, unknown.

# LEUKEMIAS IN DOGS

In dogs leukemias constitute fewer than 10% of all hemolymphatic neoplasms and are therefore considered rare. At our hospital the leukemia: lymphoma ratio is approximately 1:7 to 1:10. However, this ratio is artificially high because most dogs with lymphoma are treated by their local veterinarians, whereas most dogs with leukemia are referred for treatment. Although most leukemias in dogs are considered to be spontaneous in origin, radiation and viral particles have been identified as etiologic factors in some experimental dogs with this disease.

#### **ACUTE LEUKEMIAS**

#### **Prevalence**

Acute myeloid leukemias are more common than acute lymphoid leukemias in dogs, constituting approximately three fourths of the cases of acute leukemia. It should be remembered, however, that morphologically (i.e., as determined by evaluation of a Wright's- or Giemsa's-stained blood or bone marrow smear), most acute leukemias are initially classified as lymphoid. After cytochemical staining of the smears or immunophenotyping is performed, approximately one third to one half of them are then reclassified as myeloid. Approx-



**TABLE 81-2** 

Cytochemical Stains in Acute Leukemic Cells from Dogs and Cats

CYTOCHEMICAL STAIN	AML	AMOL	AMML	ALL
MPO	+		±	-
CAE	+	_	±	_
ANBE	_	+	±	-(+)
LIP	-	+	±	_ ` '
LAP	+		±	-(+)

AML, Acute myelogenous leukemia (AML-M<sub>0-2</sub>); AMoL, acute monoblastic/monocytic leukemia (AML-M<sub>s</sub>); AMML, acute myelomonocytic leukemia (AML-M<sub>4</sub>); ALL, acute lymphoblastic leukemia; MPO, myeloperoxidase; CAE, chloroacetate esterase; ANBE, α-naphthyl butyrate esterase; LIP, lipase; LAP, leukocyte alkaline phosphatase; +, positive; -, negative; ±, positive or negative.



**TABLE 81-3** 

Clinical Signs and Physical Examination Findings in Dogs and Cats with Acute Leukemias\*

FINDING	DOG	CAT
Clinical Sign		
Lethargy	>70	>90
Anorexia	>50	>80
Weight loss	>30-40	>40-50
Lameness	>20-30	>\$>
Persistent fever	>30-50	>\$
Vomiting/diarrhea	>20-40	>\$
Physical Examination Fi	nding	
Splenomegaly	>70	>70
Hepatomegaly	>50	>50
Lymphadenopathy	>40-50	>20-30?
Pallor	>30-60	>50-70?
Fever	>40-50	>40-60?

<sup>2</sup> Unknown

imately half of the dogs with myeloid leukemia have myelomonocytic differentiation when cytochemical staining or immunophenotyping is performed (see Table 81-2).

#### **Clinical Features**

The clinical signs and physical examination findings in dogs with acute leukemia are usually vague and nonspecific (Table 81-3). Most owners seek veterinary care when their dogs become lethargic or anorectic or when persistent or recurrent fever, weight loss, shifting limb lameness, or other nonspecific signs develop; neurologic signs occur occasionally. Some of these signs may be quite acute (e.g., days). Spleno-

<sup>\*</sup> Results are expressed as the approximate percentage of animals showing the abnormality.

megaly, hepatomegaly, pallor, fever, and mild generalized lymphadenopathy are commonly detected during routine physical examination. The spleen in these dogs is usually markedly enlarged, and it has a smooth surface on palpation. Careful inspection of the mucous membranes in dogs with acute leukemia often reveals petechiae, ecchymoses, or both, in addition to pallor. Icterus may also be detected if marked leukemic infiltration of the liver has occurred. The generalized lymphadenopathy seen in dogs with acute leukemia is usually mild, in contrast to that seen in dogs with lymphoma, in which the lymph nodes are massively enlarged. In other words, the hepatosplenomegaly is more striking than the lymphadenopathy. Most dogs with leukemia also have constitutional signs (i.e., they are clinically ill), whereas most dogs with lymphoma are asymptomatic. Although it is usually impossible to distinguish between acute myeloid and acute lymphoid leukemia on the basis of physical examination findings alone, some subtle differences do exist: Mainly, shifting limb lameness, fever, and ocular lesions are more common in dogs with acute myeloid leukemia, whereas neurologic signs are more common in dogs with acute lymphoid leukemia.

# **Hematologic Features**

Marked hematologic changes are usually present in dogs with acute leukemia. Couto (1985) and Grindem et al. (1985b) have published detailed reviews of the hematologic features of dogs with acute leukemia. Briefly, abnormal (leukemic) cells are observed in the peripheral blood of most dogs with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), although this is slightly more common in the latter (i.e., circulating blasts are absent in some dogs with AML; Fig. 81-1). Isolated cytopenias, bicytopenias, or pancytopenia is present in almost all dogs with AML and ALL. Leukoerythroblastic reactions are detected in approximately half of dogs with AML but are rare in dogs

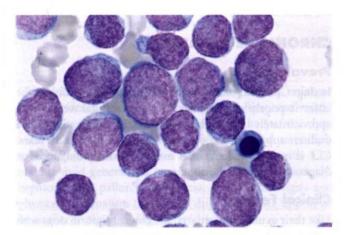


FIG 81-1
Blood smear from a dog with acute lymphoblastic leukemia and a white blood cell count of approximately 1,000,000/μl. Note the predominance of large, immature lymphoid cells with large nuclei, clumped chromatin, and nucleoli. (×1000.)

with ALL. The total white blood cell (WBC) and blast counts are highest in dogs with ALL (median, 298,200/µl; range, 4000 to 628,000/µl), and as a general rule, only dogs with ALL have WBC counts greater than 100,000/µl. Most dogs with AML and ALL are anemic, but dogs with acute monoblastic/monocytic leukemia (AMoL or AML- $M_5$ ) have the least severe anemia (packed cell volume of 30% versus 23% in all other groups). Most dogs with acute leukemias are also thrombocytopenic, although the thrombocytopenia also appears to be less severe in dogs with AML- $M_5$  (median, 102,000/µl; range, 39,000 to 133,000/µl).

# **Diagnosis**

A presumptive diagnosis in dogs with acute leukemia is usually made on the basis of the history and physical examination findings; a CBC is usually confirmatory, although the hematologic changes in dogs with "aleukemic leukemia" may resemble those of ehrlichiosis or other bone marrow disorders. To evaluate the extent of the disease, a bone marrow aspirate or biopsy is indicated. Splenic, hepatic, or lymph node aspirates for cytologic evaluation can also be obtained easily, although the information yielded may not help in establishing the diagnosis or prognosis. For example, if a dog has mild generalized lymphadenopathy and the only sample submitted to a laboratory is a lymph node, spleen, or liver aspirate, the finding of undifferentiated blasts in the smear points toward a cytologic diagnosis of either acute leukemia or lymphoma (i.e., the neoplastic lymphoid cells in lymphoma and leukemia are indistinguishable morphologically); indeed, it is quite common for the clinical pathologist to issue a diagnosis of lymphoma because it is the most common of the two diseases. In these cases, further clinical and clinicopathologic information (i.e., the degree and extent of lymphadenopathy, presence and degree of hepatosplenomegaly, hematologic and bone marrow biopsy or aspiration findings) is required to establish a definitive diagnosis.

It may be difficult to diagnose the tumor type in a dog with generalized lymphadenopathy, hepatosplenomegaly, and a low number of circulating lymphoblasts. The main differential diagnoses are ALL and lymphoma with circulating blasts (lymphosarcoma cell leukemia). It is important to differentiate between these two disorders because the prognosis for dogs with lymphoma is considerably better than that for dogs with acute leukemia. These two entities may be difficult to distinguish on the basis of the clinical, hematologic, and cytologic information obtained, but the guidelines found in Box 81-1 can be used to try to arrive at a definitive diagnosis.

When the neoplastic cells are poorly differentiated, cytochemical staining or immunophenotyping is required to establish a definitive diagnosis (see Table 81-2). This is important if the owner is contemplating treatment because the therapy and prognosis for dogs with AML are different from those for dogs with ALL (i.e., the survival time in dogs with AML is shorter than that in dogs with ALL).

In addition to lymphoma, differential diagnoses in dogs with acute or chronic leukemias include other disorders of



BOX 81-1

Acute Lymphoblastic Leukemia or Lymphoma with Circulating Blasts (Lymphosarcoma Cell Leukemia): Guidelines for a Definitive Diagnosis

- If the lymphadenopathy is massive, the dog is more likely to have lymphoma.
- If the dog is systemically ill, it is more likely to have All
- 3. If bicytopenia or pancytopenia is present, ALL is the more likely diagnosis.
- If the percentage of lymphoblasts in the bone marrow is more than 40% to 50%, the dog is more likely to have All
- 5. If hypercalcemia is present, the more likely diagnosis is lymphoma.

All, Acute lymphoblastic leukemia.



BOX 81-2

Basic Diagnostic Principles for Dogs with Suspected Leukemia

- If cytopenias or abnormal cells are present in peripheral blood, a bone marrow aspirate or biopsy specimen should be obtained.
- If the spleen or liver is enlarged, a fine-needle aspirate of the affected organs should be obtained for cytologic evaluation.
- If blasts are present, blood and bone marrow specimens should be submitted to a veterinary referral laboratory for cytochemical staining or immunophenotyping.
- Other diagnostic tests (e.g., serologic tests or polymerase chain reaction [PCR] testing for Ehrlichia canis) should be performed if appropriate.

the mononuclear-phagocytic or hematopoietic systems, such as malignant or systemic histiocytosis; systemic mast cell disease (mast cell leukemia); and infectious diseases such as ehrlichiosis, bartonellosis, mycoplasmosis, and mycobacteriosis. Box 81-2 lists the basic principles of diagnosis that apply to all dogs with suspected leukemia.

The diagnosis of acute leukemia can be extremely straightforward (i.e., a dog that is evaluated because of weight loss, lethargy, hepatosplenomegaly, pallor, and central nervous system [CNS] signs and that has a WBC of more than 500,000/µl, most of which are blasts, is most likely to have ALL), or it may represent a challenge (i.e., a dog with unexplained cytopenias of prolonged duration in which aleukemic AML-M<sub>1</sub> subsequently develops).

#### **Treatment**

The treatment of dogs with acute leukemias is usually unrewarding. Most dogs with these diseases respond poorly to therapy, and prolonged remissions are rare. Treatment failure usually stems from one or more of the following factors:

- Failure to induce remission (more common in AML than in ALL)
- 2. Failure to maintain remission
- 3. The presence or development of organ failure resulting from leukemic cell infiltration; this precludes the use of aggressive combination chemotherapy (i.e., because of enhanced toxicity)
- 4. The development of fatal sepsis, bleeding, or both caused by already existing or treatment-induced cytopenias

Prolonged remissions in dogs with AML treated with chemotherapy are extremely rare. In most dogs with AML remissions in response to any of the protocols listed in Box 81-3 are rarely observed. If animals do respond, the remission is usually extremely short-lived and survival rarely exceeds 3 months. In addition, more than half of the dogs die during induction as a result of sepsis or bleeding. Furthermore, the supportive treatment required in these patients (e.g., blood component therapy, intensive care monitoring) is financially unacceptable to most owners, and the emotional strain placed on the owner is also quite high. Therefore owners should be aware of all these factors before deciding to treat their dogs.

The prognosis may be slightly better in dogs with ALL; however, responses to treatment and survival times in these patients are considerably lower than those in dogs with lymphoma. The remission rates in dogs with ALL are approximately 20% to 40%, in contrast with those in dogs with lymphomas, which approach 90%. Survival times with chemotherapy in dogs with ALL are also shorter (average, 1 to 3 months) than those in dogs with lymphoma (average, 12 to 18 months). Untreated dogs usually live less than 2 weeks. Chemotherapy protocols used in dogs with acute leukemia are listed in Box 81-3.

# CHRONIC LEUKEMIAS

# Prevalence

In dogs CLL is far more common than CML; in addition, the latter is poorly characterized. At our hospital we evaluate approximately six to eight dogs with CLL a year, whereas we evaluate approximately one dog with CML every 3 to 5 years. CLL is one of the leukemias most commonly diagnosed at diagnostic referral laboratories.

# **Clinical Features**

Like their acute counterparts, the clinical signs in dogs with CLL or CML are vague and nonspecific; however, there is a history of chronic (i.e., months), vague clinical signs in approximately half of the dogs with chronic leukemia. Many cases of chronic leukemia are diagnosed incidentally during routine physical examination and clinicopathologic evaluation (i.e., dogs are asymptomatic). Clinical signs in dogs with



BOX 81-3

Chemotherapy Protocols for Dogs and Cats with Acute Leukemias

# Acute Lymphoblastic Leukemia

# 1. OP protocol

Vincristine, 0.5 mg/m² IV once a week
Prednisone, 40-50 mg/m² PO q24h for a week; then
20 mg/m² PO q48h

#### 2. COP protocol

Vincristine, 0.5 mg/m² IV once a week
Prednisone, 40-50 mg/m² PO q24h for a week; then
20 mg/m² PO q48h
Cyclophosphamide, 50 mg/m² PO q48h

#### 3. LOP protocol

Vincristine, 0.5 mg/m² IV once a week
Prednisone, 40-50 mg/m² PO q24h for a week; then
20 mg/m² PO q48h
L-Asparaginase, 10,000-20,000 IU/m² IM or SC once
every 2-3 weeks

#### 4. COAP protocol

Vincristine, 0.5 mg/m² IV once a week
Prednisone, 40-50 mg/m² PO q24h for a week; then
20 mg/m² PO q48h
Cyclophosphamide, 50 mg/m² PO q48h
Cytosine arabinoside, 100 mg/m² SC daily for 2-4 days\*

# Acute Myelogenous Leukemia

Cytosine arabinoside, 5-10 mg/m<sup>2</sup> SC q12h for 2-3 weeks; then on alternate weeks

Cytosine arabinoside, 100-200 mg/m² in IV drip over 4 hours

Mitoxantrone, 4-6 mg/m² in IV drip over 4 hours; repeat every 3 weeks

IV, Intravenous; PO, by mouth; IM, intramuscular; SC, subcutaneous.

CLL include lethargy, anorexia, vomiting, mildly enlarged lymph nodes, intermittent diarrhea or vomiting, and weight loss. As mentioned previously, more than half of the dogs with CLL are asymptomatic and are diagnosed serendipitously. Physical examination findings in dogs with CLL include mild generalized lymphadenopathy, splenomegaly, hepatomegaly, pallor, and pyrexia. The clinical signs and physical examination findings in dogs with CML appear to be similar to those in dogs with CLL.

A terminal event in dogs with CLL is the development of a diffuse large cell lymphoma, termed *Richter syndrome*; in humans Richter syndrome also includes prolymphocytic leukemia, acute eukemia, and Hodgkin's lymphoma. In dogs Richter syndrome is characterized by a massive, generalized lymphadenopathy and hepatosplenomegaly. Once this multicentric lymphoma develops, chemotherapy-induced, longlasting remissions are difficult to obtain and survival times are short.

Blast crisis, which involves the appearance of immature blast cells in blood and bone marrow, occurs in humans and dogs with CML months to years after the initial diagnosis is made; in humans with CLL acute leukemias are part of the Richter syndrome. In humans with blast crisis associated with CML these blasts are of either myeloid or lymphoid phenotype; the origin of the blast cell in dogs with blast crises has not been determined. Blast crises occurred in five of eleven dogs with CML described in the literature (Leifer et al., 1983). Blast crises do not appear to occur in dogs with CLL.

# **Hematologic Features**

The most common hematologic abnormality in dogs with CLL is a marked lymphocytosis resulting in leukocytosis. The lymphocytes are usually morphologically normal, although large granular lymphocytes (LGLs) are occasionally present. The lymphocyte counts range from 8000/µl to more than 100,000/µl, but lymphocyte counts of more than 500,000/µl are rare. In most dogs with CLL the neoplastic cell population is of T-cell origin. In addition to the lymphocytosis, which may be diagnostic in itself (e.g., a dog with a lymphocyte count of 100,000/µl most certainly has CLL), anemia is detected in more than 80% of the dogs and thrombocytopenia in approximately half of the dogs. Although cytologic evaluation of bone marrow aspirates in dogs with CLL usually reveals the presence of many morphologically normal lymphocytes, normal numbers of lymphocytes are occasionally detected. This is probably because the lymphocytosis in some animals with CLL stems from disorders of recirculation rather than from the increased clonal proliferation of lymphocytes in the bone marrow.

Monoclonal gammopathies have been reported in approximately two thirds of dogs with CLL in which serum was evaluated using protein electrophoresis (Leifer et al., 1986). The monoclonal component is usually IgM, but IgA and IgG components have also been reported. This monoclonal gammopathy can lead to hyperviscosity. Rarely, dogs with CLL have paraneoplastic, immune-mediated blood disorders (e.g., hemolytic anemia, thrombocytopenia, neutropenia). However, in my experience, monoclonal gammopathies are uncommon in dogs with CLL.

The hematologic features of CML in dogs are poorly characterized but include leukocytosis with a left-shift down to myelocytes (or occasionally myeloblasts), anemia, and possibly thrombocytopenia, although thrombocytosis can also occur. The hematologic findings seen during a blast crisis are indistinguishable from those seen in dogs with AML or ALL.

# Diagnosis

Absolute lymphocytosis is the major diagnostic criterion for CLL in dogs. Although other diseases (e.g., ehrlichiosis, babesiosis, leishmaniasis, Chagas' disease, Addison's disease)

<sup>\*</sup>The daily dose should be divided into two to four daily administrations.

should be considered in the differential diagnosis of dogs with mild lymphocytosis (i.e., 7000 to 20,000/µl), marked lymphocytosis (i.e., more than 20,000/µl) is almost pathognomonic for CLL. If the physical examination and hematologic abnormalities discussed in previous paragraphs (i.e., mild lymphadenopathy, splenomegaly, monoclonal gammopathy, anemia) are found, this may help establish a diagnosis of CLL in dogs with lymphocytosis, although all these changes can also be present in dogs with chronic ehrlichiosis (see Chapter 96). In patients with lymphocytosis in which a confirmatory diagnosis of CLL cannot be made, a PCR assay for clonality will typically reveal if the cells are clonal in origin. The phenotypic distribution after performing immunophenotyping may also establish if the cell population is monoclonal or polyclonal.

The diagnosis of CML may be challenging, particularly because this syndrome is poorly characterized in dogs. Some of the markers used to diagnose CML in humans are of no use in dogs. For example, the Philadelphia 1 chromosome and the alkaline phosphatase score were originally used in humans to differentiate CML from leukemoid reactions (i.e., CML cells have the Philadelphia 1 chromosome, and the alkaline phosphatase content of the neutrophils increases in the setting of leukemoid reactions and decreases in the setting of CML). Chromosamal analysis of the cells in question may reveal specific abnormalities that support a diagnosis of CML. As a general rule, a final diagnosis of CML should be made only after the clinical and hematologic findings have been carefully evaluated and the inflammatory and immune causes of neutrophilia have been ruled out.

#### **Treatment**

The clinician usually faces the dilemma of whether to treat a dog with CLL. If the dog is symptomatic, has organomegaly, or has concurrent hematologic abnormalities, treatment with an alkylator (with or without corticosteroids) is indicated. If there are no paraneoplastic syndromes (i.e., immune hemolysis or thrombocytopenia, monoclonal gammopathies), I recommend using single-agent chlorambucil at a dosage of 20 mg/m² given orally once every 2 weeks (Box 81-4). If there are paraneoplastic syndromes, the addition of corticosteroids (prednisone, 50 to 75 mg/m² by mouth [PO] q24h for 1 week, then 25 mg/m² PO q48h) may be beneficial.

Because the growth fraction of neoplastic lymphocytes in CLL appears to be low, a delayed response to therapy is common. In a high proportion of dogs with CLL treated with chlorambucil or chlorambucil and prednisone, it may take more than 1 month (and as long as 6 months) for the hematologic and physical examination abnormalities to resolve. This is in contrast to dogs with lymphoma and acute leukemias, in which remission is usually induced in 2 to 7 days.

The survival times in dogs with CLL are quite long. Indeed, even without treatment, survival times of more than 2 years are common. More than two thirds of the dogs with CLL treated with chlorambucil (with or without prednisone)



BOX 81-4

Chemotherapy Protocols for Dogs and Cats with Chronic Leukemias

#### Chronic Lymphocytic Leukemia

Chlorambucil, 20 mg/m² PO once every 2 weeks Chlorambucil as above, plus prednisone, 50 mg/m² PO q24h for a week; then 20 mg/m² PO q48h

#### COP protocol

Cyclophosphamide, 200-300 mg/m² IV once every 2 weeks

Vincristine, 0.5-0.75 mg/m<sup>2</sup> IV once every 2 weeks (alternating weeks with the cyclophosphamide)

Prednisone as in protocol 2; this treatment is continued for 6-8 weeks, at which time protocol 1 or 2 can be used for maintenance

#### Chronic Myelogenous Leukemia

Hydroxyurea, 50 mg/kg PO q24h for 1-2 weeks; then q48h

Imatinib (Gleevec), 10 mg/kg PO q24h ONLY IN CATS

PO, By mouth; IV, intravenous.

at our clinic have survived in excess of 2 years. In fact, most dogs with CLL do not die as a result of leukemia-related causes but rather of other senior disorders.

The treatment of dogs with CML using hydroxyurea (see Box 81-4) may result in prolonged remission, provided a blast crisis does not occur. However, the prognosis does not appear to be as good as that for dogs with CLL (i.e., survivals of 4 to 15 months with treatment). The treatment of blast crises is usually unrewarding. A novel therapeutic approach targeting tyrosine kinase in the neoplastic cells of humans with CML using imatinib (Gleevec) has shown to be beneficial in inducing remission; however, the drug is hepatotoxic in dogs. New small molecule tyrosine kinase inhibitors are currently under investigation in dogs with CML and other diseases associated with c-kit mutations.

#### LEUKEMIAS IN CATS

#### **ACUTE LEUKEMIAS**

#### **Prevalence**

True leukemias are rare in the cat, constituting fewer than 15% of all hematopoietic neoplasms. Although exact figures regarding the incidences of leukemias and lymphomas are not available for cats, these neoplasms are now rare.

If cytochemical staining or immunophenotyping is used to classify acute leukemias in cats, approximately two thirds are myeloid and one third are lymphoid. However, in contrast to dogs, myelomonocytic leukemias (M<sub>4</sub>) appear to be rare in cats.

Feline leukemia virus (FeLV) is commonly implicated as a cause of leukemias in cats; however, the role of feline immunodeficiency virus (FIV) in the pathogenesis of these neoplasms is still unclear. Originally, it was reported that approximately 90% of cats with lymphoid and myeloid leukemias tested positive for FeLV p27 with enzyme-linked immunosorbent assay or immunofluorescence. As discussed in Chapter 80, because the prevalence of FeLV infection is decreasing, most cats with leukemia diagnosed in our clinic over the past few years have not been viremic for FeLV (i.e., they are FeLV-negative).

#### **Clinical Features**

The clinical features and physical examination findings in cats with acute leukemias are similar to those in dogs and are summarized in Table 81-3. Shifting limb lameness and neurologic signs do not appear to be as common in cats as in dogs with myeloid leukemias.

# **Hematologic Features**

More than three fourths of cats with AML and ALL have cytopenias; leukoerythroblastic reactions are common in cats with AML but extremely rare in those with ALL. In contrast to dogs, circulating blasts appear to be more common in cats with AML than in those with ALL.

Sequential studies of cats with myeloid leukemias have revealed that the cytomorphologic features can change from one cell type to another over time (e.g., sequential diagnoses of erythremic myelosis, erythroleukemia, and acute myeloblastic leukemia are common in a given cat). This is one of the reasons that most clinical pathologists prefer the term *myeloproliferative disorder (MPD)* to refer to this leukemia in cats.

# **Diagnosis and Treatment**

The diagnostic evaluation of cats with suspected acute leukemia follows the same general sequence as that for dogs. If the changes in the CBC are not diagnostic, a bone marrow aspirate can provide information that may confirm the diagnosis (Fig. 81-2). In addition, cats with suspected or confirmed acute leukemias should be evaluated for circulating FeLV p27 and for serum antibodies against FIV.

With treatment cats with ALL apparently have better survival times than cats with AML. Survival times in cats with ALL treated with multichemotherapy range from 1 to 7 months.

There have been several published reports of cats with myeloid leukemias treated with single-agent or combination chemotherapy. The treatment protocols have included single-agent cyclophosphamide or cytosine arabinoside, as well as combinations of cyclophosphamide, cytosine arabinoside, and prednisone; cytosine arabinoside and prednisone; cyclophosphamide, vinblastine, cytosine arabinoside, and prednisone; and doxorubicin, cyclophosphamide, and prednisone. Survival times in these cats have usually ranged from 2 to 10 weeks, with a median of approximately 3 weeks. Therefore, as in dogs, intensive chemo-

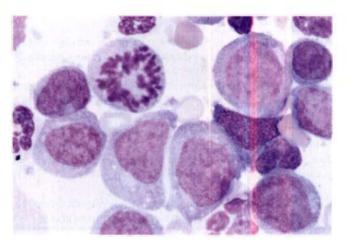


FIG 81-2
Bone marrow aspirate from a cat with peripheral blood cytopenias and absence of circulating blasts. Note the predominance of large immature myeloid cells, characterized by round to kidney-shaped nuclei. A mitotic figure is

therapy does not appear to be beneficial in cats with acute leukemias

New alternatives for the therapy of feline MPD are currently being explored. Low-dose cytosine arabinoside (LDA; 10 mg/m² subcutaneously q12h; Cytosar-U; Upjohn, Kalamazoo, Mich) has been used as an inductor of differentiation of the neoplastic clone. In several studies this treatment was observed to induce complete or partial remission in 35% to 70% of humans with MDS and MPD. Moreover, although myelosuppression was observed in some patients, the treatment was exceedingly well tolerated and associated with minimal toxicity.

We have treated several cats with MPD using LDA and have observed in most complete or partial remissions, with transient hematologic improvement. Although no major toxicities were seen, the remissions were short-lived (3 to 8 weeks).

# **CHRONIC LEUKEMIAS**

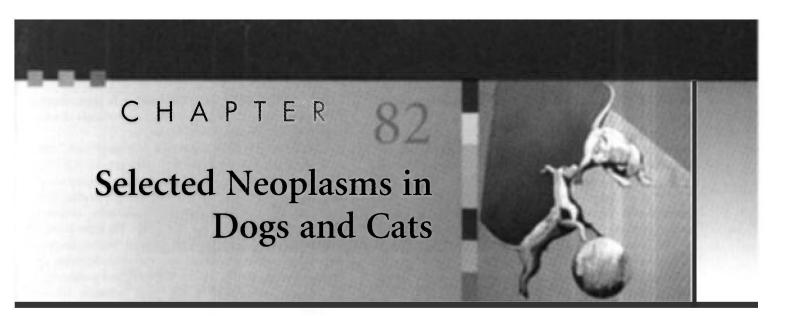
evident. (×1000.)

Chronic leukemias are are becoming more common in cats; this may be due to the relative decrease in the prevalence of acute leukemias, or it may represent a true phenomenon. CLL is occasionally found incidentally during routine physical examination. More often, cats with CLL are seen by a veterinarian because of a protracted history of vague signs of illness, including anorexia, lethargy, and gastrointestinal tract signs. In cats with CLL mature, well-differentiated lymphocytes predominate in peripheral blood and bone marrow, and the response to therapy appears to be good. In most cats with CLL the leukemic population is of T-cell origin. Most cats with CLL evaluated at our clinic showed a complete remission in response to chlorambucil with or without prednisone treatment. As in dogs, CML is poorly characterized in cats.

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# CHAPTER OUTLINE

HEMANGIOSARCOMA IN DOGS
OSTEOSARCOMA IN DOGS AND CATS
MAST CELL TUMORS IN DOGS AND CATS
Mast Cell Tumors in Dogs
Mast Cell Tumors in Cats
INJECTION SITE SARCOMAS IN CATS

# HEMANGIOSARCOMA IN DOGS

Hemangiosarcomas (HSAs, hemangioendotheliomas, angiosarcomas) are malignant neoplasms that originate from the vascular endothelium. They occur predominantly in older dogs (8 to 10 years of age) and in males; German Shepherd Dogs and Golden Retrievers are at high risk for this neoplasm.

The spleen, right atrium, and subcutis are common sites of involvement at the time of presentation. Approximately 50% of the tumors originate in the spleen, 25% in the right atrium, 13% in subcutaneous tissue, 5% in the liver, 5% in the liver-spleen–right atrium, and 1% to 2% simultaneously in other organs (i.e., kidney, urinary bladder, bone, tongue, prostate). The latter are referred to as *multiple tumor*, *undeterminable primary*. In Greyhounds most of the HSAs evaluated have been intramuscular.

In general, the biologic behavior of this neoplasm is highly aggressive, with most anatomic forms of the tumor infiltrating and metastasizing early in the disease. The exception are primary dermal and conjunctival or third eyelid HSAs, which have a low metastatic potential.

# **Clinical and Clinicopathologic Features**

The nature of owners' complaints and the clinical signs at presentation are usually related to the site of origin of the primary tumor; to the presence or absence of metastatic lesions; and to the development of spontaneous tumor rupture, coagulopathies, or cardiac arrhythmias. More than half of the dogs with HSA are evaluated because of acute collapse after spontaneous rupture of the primary tumor or a metastatic lesion. Some episodes of collapse may stem from ventricular arrhythmias, which are relatively common in dogs with splenic or cardiac HSA. In addition, dogs with splenic HSA often are seen because of abdominal distention secondary to tumor growth or hemoabdomen.

Dogs with cardiac HSA usually are presented for evaluation of right-sided congestive heart failure (caused by cardiac tamponade or obstruction of the posterior vena cava by a neoplasm) or cardiac arrhythmias (see the chapters on cardiovascular system disorders for additional information). Dogs with cutaneous or subcutaneous neoplasms are usually evaluated because of a lump. Greyhounds with intramuscular HSA typically present with a swollen and bruised rear limb; the tumor is frequently in the biceps femoris or quadriceps.

Two common problems in dogs with HSA, regardless of the primary location or stage, are anemia and spontaneous bleeding. The anemia is usually the result of intracavitary bleeding or microangiopathic hemolysis (MAHA), whereas the spontaneous bleeding is usually caused by disseminated intravascular coagulation (DIC) or thrombocytopenia secondary to MAHA (see later discussion). HSA is so highly associated with clinical DIC (see Chapter 87) that at our hospital dogs with DIC of acute onset but without an obvious primary cause are evaluated for HSA first.

Hemangiosarcomas are usually associated with a wide variety of hematologic and hemostatic abnormalities. Hematologic abnormalities in dogs with HSA have been well characterized and include anemia; thrombocytopenia; the presence of nucleated red blood cells (RBCs), RBC fragments (schistocytes), and acanthocytes in the blood smear; and leukocytosis with neutrophilia, a left shift, and monocytosis. In addition, hemostatic abnormalities are also common in dogs with HSAs. However, these hematologic abnormalities are location dependent; for example, in our clinic anemia, thrombocytopenia, schistocytosis, and acanthocytosis were significantly more common in dogs with splenic, right atrial,

or visceral HSA than in dogs with subcutaneous or dermal HSA (Alvarez et al., 2006).

Most dogs with HSA (83%) evaluated at our clinic were anemic; more than one half had RBC fragmentation and acanthocytosis (Hammer et al., 1991b). The pretreatment coagulograms of these dogs were normal in only four dogs (17%). Most dogs (75%) had thrombocytopenia, with a mean platelet count of 137,000/µl. Approximately one half of the coagulograms met three or more criteria for diagnosis of DIC, whereas fewer than 12% of them were compatible with microangiopathic thrombocytopenia. Approximately 25% of these dogs died as a result of their hemostatic abnormalities.

# **Diagnosis**

Hemangiosarcomas can be diagnosed cytologically on the basis of the appearance of fine-needle aspirates (FNA) or impression smears. The neoplastic cells are similar to those in other sarcomas in that they are spindle-shaped or polybedral; however, they are quite large; have large nuclei with a lacy chromatin pattern and one or more nucleoli; and a bluish gray, usually vacuolated cytoplasm (Fig. 82-1). Nucleated RBCs are frequently present cytologically in HSAs. Although HSA cells are relatively easy to identify in tissue aspirates or impression smears, they are extremely difficult to identify in HSA-associated effusions. The probability of establishing a cytologic diagnosis of HSA after evaluating effusions is less than 25%. A further problem with effusions is that a specimen may contain reactive mesothelial cells that may resemble neoplastic cells, leading to a false-positive diagnosis of HSA.

In general, a presumptive clinical or cytologic diagnosis of HSA should be confirmed histopathologically. Because of the large size of some splenic HSAs, however, multiple samples (from different morphologic areas) should be submitted in appropriate fixative. Histochemically, HSA cells are

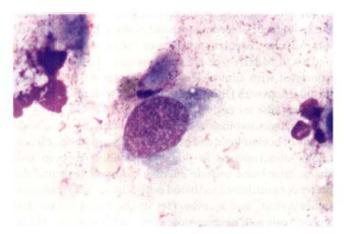


FIG 82-1
Cytologic features of canine hemangiosarcoma. Note the spindle-shaped cells, with a dark, vacuolated cytoplasm, and the fine nuclear chromatin pattern with prominent nucleolus. (×1000.)

positive for von Willebrand factor antigen in approximately 90% of the cases; CD31 is a relatively new marker of endothelial origin positive in most HSAs.

Metastatic sites can be detected radiographically, ultrasonographically, or on computed tomography (CT). Our routine staging system for dogs with HSA includes a complete blood count (CBC), serum biochemistry profile, hemostasis screen, urinalysis, thoracic radiographs, abdominal ultrasonography, and echocardiography. The latter is used to identify cardiac masses and determine the baseline fractional shortening before instituting doxorubicin-containing chemotherapy (see the section on treatment and prognosis).

Thoracic radiographs in dogs with metastatic HSA are typically characterized by the presence of interstitial or alveolar infiltrates, as opposed to the common "cannonball" metastatic lesions seen with other tumors. The radiographic pattern may be due to true metastases or to DIC and intrapulmonary bleeding, or adult respiratory distress syndrome (ARDS).

Ultrasonography constitutes a reliable way to evaluate dogs with suspected or confirmed HSA for intraabdominal disease. Neoplastic lesions appear as nodules with variable echogenicity, ranging from anechoic to hyperechoic (Fig. 82-2). Hepatic metastatic lesions can often be identified using this imaging technique. However, the clinician should bear in mind that what appear to be metastatic nodules in the liver of a dog with a splenic mass may represent regenerative hyperplasia rather than true metastatic lesions. Contrast ultrasonography appears to enhance the operator's ability to detect hepatic metastatic nodules from HSA.

# **Treatment and Prognosis**

Historically, the mainstay of treatment for dogs with HSA has been surgery, although the results have been poor. Survival times vary with the location and stage of the tumor, but in general (with the exception of dermal and conjunctival or third eyelid HSAs), they are quite short (approximately 20 to 60 days, with a 1-year survival rate of <10%). Results of treatment combining surgery and postoperative adjuvant



FIG 82-2 Ultrasonogram of an intraabdominal hemangiosarcoma.

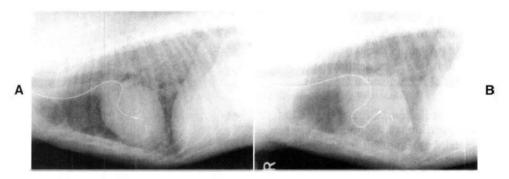


FIG 82-3

Thoracic radiographs of a 10-year-old, spayed female German Shepherd Dog with pulmonary metastases from a primary splenic hemangiosarcoma before **(A)** and 9 weeks after initiating VAC chemotherapy **(B)**. Notice the complete disappearance of the pulmonary nodules. The radiopaque line is the lead of a permanent pacemaker.

chemotherapy with doxorubicin; doxorubicin and cyclophosphamide (AC protocol); and vincristine, doxorubicin, and cyclophosphamide (VAC protocol) are better than with surgery alone. Median survival times range from 140 to 202 days.

The median survival times of dogs with HSA treated with the VAC protocol (see box on cancer chemotherapy protocols in Chapter 81) are approximately 190 days, with a 30% 1-year survival rate. Interestingly, in a recent study conducted in our clinic, the presence of metastasis was not a negative prognostic factor in dogs with HSA receiving VAC chemotherapy (Alvarez et al., 2007). Dogs with metastatic HSA had a 70% response rate (Fig. 82-3). Adverse effects associated with this protocol include myelosuppression, gastroenteritis, alopecia and hyperpigmentation, and cardiotoxicity. There was no apparent difference in the survival times between dogs with bulky disease (i.e., no surgical cytoreduction) and those that had undergone surgery. Similar results were reported for dogs treated either with doxorubicin and cyclophosphamide or with doxorubicin alone; however, in my experience, the prognosis for dogs with HSA is better if a three-drug combination, instead of a two-drug combination or monochemotherapy, is used. In our clinic we have rarely been able to administer more than 3 or 4 doses of single agent doxorubicin in dogs with HSA because they have already relapsed. The coagulopathies in HSA patients should be managed simultaneously, as discussed in Chapter 85.

Biologic response modifiers and antiangiogenic factors have also been used in dogs with HSA in combination with doxorubicin-containing chemotherapy. Dogs receiving liposome-encapsulated MTP (muramyl tripeptide—the active immunomodulatory molecule in bacille Calmette-Guerin [BCG]) and AC chemotherapy after splenectomy for HSA had significantly longer survival times (277 days) than those receiving chemotherapy and placebo (144 days; Vail et al., 1995). However, liposomal MTP is not readily available to the practicing veterinarian. Recently, minocycline, an antiangiogenic antibiotic, used at a dosage of 5 mg/kg by mouth every 24 hours, was added to the AC protocol in dogs with HSA (Sorenmo et al., 2000); the median survival time was

170 days, similar to the median survival times obtained when using chemotherapy alone.

In summary, HSAs are usually diagnosed on the basis of historical, physical examination, and clinicopathologic findings, in conjunction with ultrasonographic and radiographic changes. A morphologic diagnosis can usually be made on the basis of cytologic or histopathologic findings. Although surgery is the preferred treatment, survival times in such animals are extremely short (except in dogs with dermal or conjunctival/third eyelid HSA). Postoperative adjuvant chemotherapy using doxorubicin-containing protocols prolongs survival in dogs with this malignancy.

# OSTEOSARCOMA IN DOGS AND CATS

# **Etiology and Epidemiology**

Primary bone neoplasms are relatively common in dogs but rare in cats. Most primary bone tumors in dogs are malignant in that they usually cause death as a result of local infiltration (e.g., pathologic fractures or extreme pain leading to euthanasia) or metastasis (e.g., pulmonary metastases in osteosarcoma [OSA]). In cats most primary bone neoplasms, although histologically malignant, are cured by wide surgical excision (i.e., amputation). Neoplasms that metastasize to the bone are rare in dogs; some that occasionally metastasize to bones in dogs are transitional cell carcinoma of the urinary tract, osteosarcoma of the appendicular skeleton, hemangiosarcoma, mammary adenocarcinoma, and prostatic adenocarcinoma. Bone metastases are exceedingly rare in cats.

Osteosarcomas are the most common primary bone neoplasm in dogs. They can affect either the appendicular or axial skeletons, and they occur primarily in large- and giantbreed dogs and in Greyhounds; they are common in middleage to older dogs. There is a distinct genetic predisposition to OSA in dogs; for example, in former racing Greyhounds OSA is the most common cause of death (i.e.; 25%), whereas OSAs are extremely rare in show Greyhounds in the U.S. The biologic behavior of OSA is characterized by aggressive local infiltration of the surrounding tissues and rapid hematogenous dissemination (usually to the lungs). Although historically it was believed that OSAs of the axial skeleton had a low metastatic potential, it now appears that their metastatic rate is similar to that of the appendicular OSAs.

#### **Clinical Features**

Appendicular OSAs occur predominantly in the metaphyses of the distal radius, distal femur, and proximal humerus, although other metaphyses can also be affected. As just mentioned, they typically affect Greyhounds and male dogs of large (and giant) breeds, and owners seek veterinary care because of lameness or swelling of the affected limb. Physical examination usually reveals a painful swelling in the affected area, with or without soft tissue involvement. The pain and swelling can be acute in onset, leading to the presumptive diagnosis of a nonneoplastic orthopedic problem and thus considerably delaying diagnosis and definitive therapy for the neoplasm. Pathologic fractures are common in Greyhounds with OSA but rare in other breeds.

# **Diagnosis**

Radiographically, OSAs exhibit a mixed lytic-proliferative pattern in the metaphyseal region of the affected bone (Fig. 82-4). Adjacent periosteal bone formation leads to the development of the so-called Codman's triangle, which is composed of the cortex in the affected area and the periosteal proliferation. OSAs typically do not cross the articular space, but occasionally they can infiltrate adjacent bone (e.g., ulnar lysis resulting from an adjacent radial OSA). Because other primary bone neoplasms and some osteomyelitis lesions can mimic the radiographic features of OSAs, cytology or biopsy specimens of every lytic or lytic-proliferative bone lesion should be obtained before the owners decide on a specific treatment. An exception to this rule is an owner who has already decided that amputation is the initial treatment of choice for that lesion (i.e., the limb is amputated and the lesion is submitted for histopathologic evaluation).

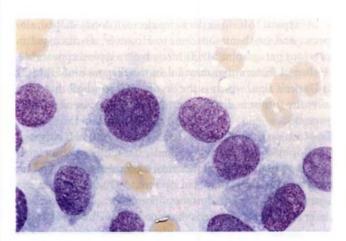
Once a presumptive radiographic diagnosis has been established and if the owners are contemplating treatment, thoracic and/or bone (i.e., skeletal survey) radiographs should be obtained to determine the extent of the disease. We usually obtain three radiographic views of the thorax and do not perform a skeletal radiographic survey (or radionuclide bone scan). Fewer than 10% of dogs with OSA initially have radiographically detectable lung lesions; the presence of metastases is a strong negative prognostic factor.

The radiographic diagnosis can be confirmed before surgery (i.e., limb amputation or limb salvage) on the basis of the findings yielded either by FNA or by aspiration of the affected area using a bone marrow aspiration needle. In most cases a blind percutaneous FNA can be performed with only manual restraint; if the operator cannot penetrate through the cortex, ultrasonographic guidance almost always allows visualization of a "window" through which the needle is inserted. OSA cells are usually round or oval; have distinct



FIG 82-4
Radiographic appearance of a typical osteosarcoma of the radius in a dog. Note the lytic and proliferative changes characteristic of this neoplasm. (Courtesy RM Gamblin.)

cytoplasmic borders; have a bright blue, granular cytoplasm; and have eccentric nuclei with or without nucleoli (Fig. 82-5); multinucelatedgiant cells are common, and there is frequenly pink amorphous material (osteoid) in the background or in the cytoplasm of the osteoblasts. If the round cells cannot be convincingly identified as osteoblast, most diagnostic laboratories can perform an alkaline phosphatase (ALP) cytochemical stain in unstained slides; osteoblasts are typically ALP-positive. A preamputation diagnosis can also be made after histopathologic evaluation of core biopsy specimens from the affected areas. To obtain a bone biopsy, a 13- or 11-gauge Jamshidi bone marrow biopsy needle (Monoject) is used with the animal under general anesthesia, and a minimum of two (and preferably three) cores of tissue are obtained from both the center of the lesion and the area between affected and unaffected bone. The diagnostic yield of this procedure is quite high (approximately 70% to 75%). In our clinic we obtain cytologic diagnoses in the vast majority of patients with OSA; we rarely need to perform a biopsy in order to confirm a diagnosis.



Characteristic cytologic features of osteosarcoma in a fineneedle aspirate of a lytic/proliferative lesion in the proximal scapula of a 12-year-old Wirehaired Terrier. Note the round to oval eccentric nuclei with a fine chromatin pattern and prominent nucleoli. (×1000.)

As long as the owners understand the biologic behavior of the neoplasm (i.e., the high likelihood of their dog dying of metastatic lung disease within 4 to 6 months of amputation if no chemotherapy is used) and as long as the clinical and radiographic features of the lesion are highly suggestive of OSA, the limb can be amputated in the absence of a histopathologic diagnosis. The amputated leg (or representative samples) and the regional lymph nodes should always be submitted for histopathologic evaluation. The presence of pulmonary or lymph node metastases is a negative prognostic factor for survival in dogs with OSA.

# **Treatment and Prognosis**

The treatment of choice for dogs with OSA is amputation with adjuvant single-agent or combination chemotherapy. The median survival time in dogs with appendicular OSA treated with amputation alone is approximately 4 months, whereas in dogs treated with amputation and cisplatin, amputation and carboplatin, amputation and doxorubicin, or amputation and combination chemotherapy it is approximately 1 year. The dosages for chemotherapy in dogs with OSA are given in the box on cancer chemotherapy protocols at the end of this chapter and Box 82-1. At our hospital we use either doxorubicin or carboplatin immediately after amputation for a total of five and four treatments, respectively. With the advent of generic carboplatin, the cost is now acceptable to most owners.

An alternative therapeutic approach for dogs with distal radial or ulnar OSAs consists of sparing the limb in affected dogs. Instead of amputation, the affected bone is resected and an allograft from a cadaver (or a prosthetic device) is used to replace the neoplastic bone; novel biomaterials are also currently being investigated for this purpose. The dogs are also treated with intravenous (IV) chemotherapy and, in



# BOX 82-1

Chemotherapy Protocols and Palliative Treatment for Dogs with Osteosarcoma

#### **Chemotherapy Protocols**

- 1. Carboplatin: 300 mg/m<sup>2</sup>, IV, q3 weeks for 4-6 doses
- Doxorubicin: 30 mg/m², IV, q2 weeks, for 5 doses
   Carboplatin: 300 mg/m², IV, on weeks 1 and 6 plus Doxorubicin: 30 mg/m<sup>2</sup>, IV, on weeks 3 and 9.

#### **Palliative Treatment**

- 1. Pamidronate: 1-2 mg/kg, IV CRI in 0.9% saline, over 1-2 hours, q2-4 weeks
- 2. Tramadol (Ultram®): 1-2 mg/kg, PO, q8-12h
- 3. Deracoxib (Deramaxx®): 1-2 mg/kg, PO, q24h\*

general, have almost normal limb function. Survival times in dogs treated with limb-sparing procedures are comparable to those in dogs that undergo amputation plus chemotherapy, with the added benefit to the owners of having a fourlegged pet. The main complication is the development of osteomyelitis in the allograft; if that occurs, the limb frequently needs to be amputated. However, in patients with infected allografts that eventually undergo amputation, the survival times are significantly longer than in dogs that did not experience complications (Lascelles et al., 2005).

If owners are reluctant to allow the veterinarian to amputate the limb, local radiotherapy plus chemotherapy may be beneficial. We usually avoid using doxorubicin as the chemotheraputic agent to prevent radiosensitization and severe cutaneous reactions to irradiation. In addition to radiation therapy, we use bisphosphonates (pamidronate 1-2 mg/kg, IV constant rate infusion, q2-4 weeks) and analgesics (see Box 82-1) for pain control and palliative care.

Chemotherapy may modify the biologic behavior of the tumor, resulting in a higher prevalence of bone metastases and a lower prevalence of pulmonary metastases. Moreover, the doubling time (i.e., growth rate) of metastatic lesions appears to be longer than that in dogs that have not received chemotherapy, and there appear to be fewer metastatic nodules in treated than in untreated dogs. Therefore surgical removal of the metastatic nodules (i.e., metastasectomy) followed by additional chemotherapy may be recommended for a dog that has been treated with chemotherapy after amputation of the limb and in which one to three pulmonary metastatic lesions are detected (O'Brien et al., 1993).

As discussed in previous paragraphs, the treatment of choice for OSAs in cats is limb amputation alone. Extremely long survival times (in excess of 2 years) are common in such cats. As discussed in Chapter 69, cisplatin is extremely toxic in cats and should therefore not be used in this species. If necessary, carboplatin or doxorubicin can be used instead.

<sup>\*</sup>Other nonsteroidal antiinflamatories are also effective. IV, Intravenous; CRI, continuous rate infusion; PO, by mouth.

# MAST CELL TUMORS IN DOGS AND CATS

Not one of them is like the other, don't ask me why, please ask your mother.

From One Fish, Two Fish, Red Fish, Blue Fish, by Dr. Seuss

Mast cell tumors (MCTs) are among the most common skin tumors in dogs and are relatively common in cats. They originate from mast cells, which are intimately involved in the local control of vascular tone and which contain a large array of intracytoplasmic bioactive molecules, including heparin, histamine, leukotrienes, and several cytokines. Given their unpredictable biologic behavior, the term *mast cell tumor* is preferred to *mastocytoma* or *mast cell sarcoma*. Because of differences in the clinical and pathologic features of canine and feline MCTs, they are discussed separately.

# MAST CELL TUMORS IN DOGS

# **Etiology and Epidemiology**

MCTs constitute approximately 20% to 25% of the skin and subcutaneous tumors seen by practicing veterinarians. Brachiocephalic breeds (Boxer, Boston Terrier, Bull Mastiff, English Bulldog) are at high risk for MCTs. These tumors are also more common in middle-age to older dogs (mean age, approximately 8.5 years) than in younger dogs, but there is no gender-related predilection. MCTs have been found in sites of chronic inflammation or injury, such as burn scars.

# **Clinical and Pathologic Features**

MCTs occur either as dermoepidermal masses (i.e., a superficial mass that moves with the skin) or subcutaneous masses (i.e., the overlying skin moves freely over the tumor). Grossly, MCTs can mimic any primary or secondary skin lesion, including a macula, papula, nodule, tumor, and crust. Approximately 10% to 15% of all MCTs in dogs are clinically indistinguishable from the common subcutaneous lipomas. As a rule, an MCT cannot be definitively diagnosed until the lesion has been evaluated cytologically or histopathologically.

Most MCTs are solitary, although multifocal MCTs can occur in dogs. Regional lymphadenopathy caused by metastatic disease is also common in dogs with invasive MCTs. Occasionally, splenomegaly or hepatomegaly is present in dogs with systemic dissemination.

Given the fact that mast cells produce a variety of bioactive (mainly vasoactive) substances, dogs with MCTs may be evaluated because of diffuse swelling (i.e., edema and inflammation around a primary tumor or its metastatic lesion), erythema, or bruising of the affected area. These episodes may be acute, and they may occur during or shortly after exercise or exposure to cold weather. Percutaneous FNA of an unexplained subcutaneous swelling in dogs should always be performed as part of the workup.

A "typical" MCT is a dermoepidermal, dome-shaped, alopecic, and erythematous lesion. However, as discussed in previous paragraphs, MCTs rarely have a typical appearance. A clinical feature that may aid in the diagnosis of an MCT is Darier's sign, which is the crythema and wheal that form after the tumor is slightly traumatized (i.e., scraped or compressed).

Most dogs with MCTs have a normal CBC, although eosinophilia (sometimes marked), basophilia, mastocythemia, neutrophilia, thrombocytosis, or anemia (or a combination of these) may be present. Serum biochemistry abnormalities are uncommon.

From a histopathologic standpoint, MCTs are traditionally classified into three categories: well differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3). Several studies have shown that dogs with grade 1 tumors treated with surgery or radiotherapy have longer survival times than identically treated dogs with grade 3 tumors, mainly because well-differentiated neoplasms have a lower metastatic potential (i.e., most tumors in dogs with systemic mast cell disease are grade 3). Special stains may be required to identify the typical intracytoplasmic granules in poorly differentiated neoplasms. The mitotic index is of prognostic relevance in dogs with MCTs, so it should be provided by the pathologist (Romansik et al., 2007). In addition to the grading of the tumor, the pathologist should provide the clinician with information regarding the completeness of the excision. A dog with an incompletely excised MCT is rarely cured by the initial surgical procedure and requires either a second surgery or irradiation of the affected area.

From a molecular standpoint, a variable percentage of canine MCTs have c-kit mutations; c-kit is the stem cell growth factor receptor, and its mutation results in immortalized clones that do not undergo apoptosis (Jones et al., 2004).

# **Biologic Behavior**

The biologic behavior of canine MCTs can be summed up in one word: unpredictable. Even though several criteria may help in establishing the biologic behavior of these neoplasms, they rarely apply to an individual dog (i.e., they may be meaningful from the statistical viewpoint).

In general, well-differentiated (grade 1), solitary cutaneous MCTs have a low metastatic potential and low potential for systemic dissemination. However, the clinician may encounter a dog with several dozen cutaneous MCTs, which on histopathologic evaluation are well differentiated.

Grade 2 and 3 tumors have a higher metastatic potential and a higher potential for systemic dissemination than grade 1 MCTs. Metastases to the regional lymph nodes commonly occur (particularly in dogs with grade 3 tumors), although occasionally a tumor "skips" the draining lymph node and metastasizes to the second or third regional node (e.g., a digital MCT in the rear limb metastasizing to the iliac or sublumbar node). Because nodal metastases can be present in normal-size lymph nodes, every lymph node in the region

of an MCT should be aspirated regardless of whether it is enlarged or not. Pulmonary metastases are extremely rare. Although not evident from published clinical data, it appears that MCTs in certain anatomic locations are more aggressive than tumors in other areas. For example, distal limb (e.g., toe), perineal, inguinal, and extracutaneous (e.g., oropharyngeal, intranasal) MCTs appear to have a higher metastatic potential than similarly graded tumors in other regions (e.g., trunk, neck).

Another biologic characteristic of canine MCTs is that they may become systemic, behaving like a hematopoietic malignancy (i.e., a lymphoma or leukemia). These dogs usually have a history of a cutaneous MCT that was excised. Most dogs with systemic mast cell disease (SMCD) are evaluated because of lethargy, anorexia, vomiting, and weight loss in association with splenomegaly, hepatomegaly, pallor, and (occasionally) detectable cutaneous masses. The CBC in affected dogs commonly reveals cytopenias, with or without circulating mast cells.

MCTs can release bioactive substances that may cause edema, erythema, or bruising of the affected area. Gastrointestinal tract ulceration may also occur as a result of hyperhistaminemia (approximately 80% of dogs euthanized because of advanced MCTs have gastroduodenal ulceration). Therefore any dog with an MCT should undergo occult fecal blood testing. Profuse intraoperative and postoperative bleeding and delayed wound healing occur in some dogs as a consequence of the bioactive substances released from mast cells.

# Diagnosis

The evaluation of a dog with a suspected MCT should include FNA of the affected area. MCTs are extremely easy to diagnose cytologically. They consist of a monomorphic population of round cells with prominent intracytoplasmic purple granules; eosinophils are frequently present in the smear (see Fig. 75-6). In approximately one third of MCTs, the granules do not stain with Diff-Quik; hence if agranular round cells are found in a dermal or subcutaneous mass resembling an MCT, the clinician should stain the slide with Giemsa or Wright's stain to reveal the characteristic purple granules. A cytologic diagnosis of MCT allows the clinician to discuss treatment options with the owner and to plan therapeutic strategies (see the section on treatment and prognosis).

Although clinical pathologists frequently state the degree of differentiation of the cells in a cytologic specimen of an MCT, that scheme does not necessarily correlate with the histopathologic grading system. In other words, a cytologic diagnosis of a well-differentiated MCT does not necessarily imply that it will be a grade 1 tumor when evaluated histopathologically (i.e., cytologic grading may not have the same prognostic implications as histopathologic grading).

The clinical evaluation of a dog with a cytologically confirmed MCT should include careful palpation of the affected area and its draining lymph nodes; abdominal palpation, radiography, or ultrasonography to search for hepatosplenomegaly; a CBC, serum biochemistry profile, and urinalysis; and thoracic radiography if the neoplasm is in the anterior one half of the body (i.e., to detect intrathoracic lymphadenopathy). If lymphadenopathy, hepatomegaly, or splenomegaly is present, FNA of the enlarged lymph node or organ should be performed to detect mast cells (i.e., local neoplasm versus metastatic tumor versus SMCD).

The use of a buffy coat smear to search for circulating mast cells is controversial. It was thought that the presence of mast cells in a buffy coat smear indicated systemic dissemination and therefore a poor prognosis. However, dogs with a solitary, potentially curable MCT occasionally have low numbers of circulating mast cells that disappear from circulation shortly after the primary tumor is excised or irradiated. Moreover, a recent study revealed that circulating mast cells are more common in dogs with diseases other than MCTs; over 95% of the CBCs with circulating mast cells were from dogs with inflammatory disorders, regenerative anemia, tumors other than MCTs, and trauma (McManus, 1999). Also, dogs with MCT had significantly lower circulating mast cell counts (71 per buffy coat smear) than those with other diseases (276 per buffy coat smear). Cytologic evaluation of a bone marrow aspirate may therefore be more beneficial for staging purposes. Dogs with more than five mast cells per 500 nucleated cells are believed to have SMCD; however, bone marrow mast cells have also been documented to disappear after excision or irradiation of the primary tumor. Therefore the appropriate staging procedures in dogs with MCTs remains controversial. At our clinic we do not use buffy coat smears or bone marrow aspirates routinely in dogs with MCT and a normal CBC; if cytopenias or leukoerythroblastic reactions are present, we perform a bone marrow aspirate.

As discussed previously, all dogs with MCTs should be tested for occult blood in the stool even if melena is not evident. There are several kits for this purpose. The presence of blood in the stool is suggestive of upper gastrointestinal tract bleeding. If this is found on repeat testing, the dog should be treated with H<sub>2</sub> antihistamines (i.e., famotidine, ranitidine) with or without a coating agent (i.e., sucralfate; see Chapter 30). Once this clinical information is obtained, the tumor should be staged to determine the extent of disease (Table 82-1).

# **Treatment and Prognosis**

As discussed previously, it is imperative to know whether the mass the clinician is preparing to excise is an MCT because this information is useful when discussing treatment options with the client and when planning the treatment strategy. Dogs with MCT can be treated with surgery, radiotherapy, chemotherapy, or a combination of these. However, the first two treatment options are potentially curative, whereas chemotherapy is usually only palliative. Treatment guidelines are provided in Table 82-2.

A solitary MCT in an area in which complete surgical excision is feasible should be removed by aggressive en bloc resection (i.e., 2- to 3-cm margins around and underneath

the tumor). If a complete excision is obtained (according to the pathologist evaluating the specimen), the tumor is grade 1 or 2, and no metastatic lesions are present; there is usually no need for further treatment (i.e., the dog is most likely cured). If the excision appears incomplete, the clinician can take one of three courses of action: (1) perform a second surgery in an attempt to excise the remaining tumor (the excised area should be submitted for histopathologic evaluation to assess the completeness of excision); (2) irradiate the surgical site (35 to 40 Gy delivered in 10 to 12 fractions); or (3) administer a short course (3-6 months) of lomustine chemotherapy (discussed later). The three options appear to be equally effective, resulting in approximately an 80% probability of long-term survival.

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**TABLE 82-1** 

Clinical Staging Scheme for Dogs with Mast Cell Tumors

STAGE	DESCRIPTION
	One tumor confined to the dermis without
	regional lymph node involvement
	<ul> <li>a. Without systemic signs</li> </ul>
	b. With systemic signs
П	One tumor confined to the dermis with
	regional lymph node involvement
	a. Without systemic signs
	b. With systemic signs
111	Multiple dermal tumors or a large infiltrating
	tumor with or without regional lymph node
	involvement
	a. Without systemic signs
	b. With systemic signs
IV	Any tumor with distant metastases or
	recurrence with metastases
	a. Without systemic signs
	b. With systemic signs

A solitary MCT in an area in which surgical excision is difficult or impossible, or at a site where the cosmetic or functional results are unacceptable (e.g., prepuce, eyelid), can be successfully treated with radiotherapy. Approximately two thirds of dogs with a grade 1 or 2 localized MCT treated with radiotherapy alone are cured. Irradiation is also recommended for the management of tumors in high-risk areas. Intralesional injections of corticosteroids (triamcinolone [Vetalog], 1 mg intralesionally per centimeter of tumor diameter q2-3 weeks) can also successfully shrink the tumor (although it is usually only palliative). Intralesional injections of deionized water have also been reported to be beneficial in managing local MCTs, although that has not been my experience. An alternative approach is to use neodajuvant chemotherapy (ie; chemotherapy before and after surgery). In these dogs a combination of lomustine and prednisone is used, with or without vinblastine, in order to decrease the tumor size; then surgery is performed, followed by chemotherapy (discussed later).

Once metastatic or disseminated MCTs (or SMCD) develop, a cure is rarely obtained. Treatment in these dogs consists of chemotherapy and supportive therapy and is aimed at palliating the neoplasm and its complications. Results of prospective studies of chemotherapy in dogs with MCTs have not been very encouraging; two chemotherapy protocols have been widely used (see box on cancer chemotherapy protocols at the end of this chapter): (1) prednisone and (2) the CVP protocol (cyclophosphamide, prednisone, vinblastine). Over the past several years, lomustine (CCNU) has been used with a high degree of success in dogs with nonresectable, metastatic, or systemic MCTs. The probability of response is high (>50%), and remissions in excess of 18 months in dogs with metastatic grade 2 and 3 MCTs have been documented. Lomustine can be combined with prednisone, vinblastine, or both (see Table 82-2).

Traditionally, I used lomustine, with or without prednisone (see Table 82-2), and famotidine and/or sucralfate in dogs with metastatic or nonresectable MCTs. Although



TABLE 82-2

Treatment Guidelines for Dogs with Mast Cell Tumors

STAGE	GRADE	RECOMMENDED TREATMENT	FOLLOW-UP
1	1, 2	Surgical excision	Complete→observe Incomplete→second surgery or radiotherapy
1	3	Chemotherapy*	Continue chemotherapy
11	1, 2, 3	Surgical excision or radiotherapy	CCNU and prednisone (see below)*
III, IV	1, 2, 3	Chemotherapy*	Continue chemotherapy
Chemothe	erapy protoco	ols for dogs with mast cell tumors:	

1. Prednisone, 50 mg/m² by mouth (PO) q24h for 1 week; then 20-25 mg/m² PO q48h indefinitely plus lomustine (CCNU, Ceenu), 60 mg/m² PO q3 weeks.

Prednisone, 50 mg/m² by mouth (PO) q24h for 1 week; then 20-25 mg/m² PO q48h indefinitely plus lomustine (CCNU, Ceenu), 60 mg/m² PO q6 weeks, alternating doses with vinblastine, 2 mg/m², IV, q6 weeks (the dog receives lomustine, 3 weeks later vinblastine, 3 weeks later lomustine again, and so on)

<sup>\*</sup> For more information, see box at the end of this chapter.

lomustine is potentially myelosuppressive, clinically relevant cytopenias are rare; however, hepatotoxicity is common (see Chapter 78), so chemistry profiles should be evaluated periodically. The addition of vinblastine allows administration of lomustine every 6 weeks instead of every 3 weeks; this may decrease the prevalence of hepatotoxicity.

Small molecule tyrosine kinase inhibitors have demonstrated efficacy against some canine MCTs with c-kit mutations and will likely be available in the near future (Pryer et al., 2003; London et al., 2003)

#### MAST CELL TUMORS IN CATS

#### **Etiology and Epidemiology**

Although MCTs are relatively common in cats, they rarely result in the considerable clinical problems seen in dogs with this neoplasm. Most cats with MCTs are middle-age or older (median, 10 years old), there is apparently no gender-related predilection, and Siamese cats may be at high risk. Feline leukemia virus and feline immunodeficiency virus do not play a role in the development of this tumor.

As opposed to the dog, in which most of the MCTs are cutaneous or subcutaneous, cats exhibit two main forms of feline MCTs: visceral and cutaneous. There is controversy as to whether cutaneous forms are more common than visceral forms and whether both forms can co-exist in the same cat. At our clinic the cutaneous form is considerably more common than the visceral form, and it is extremely rare for the cutaneous and visceral forms to coexist.

#### **Clinical and Pathologic Features**

Visceral MCTs are characterized by either hemolymphatic or intestinal involvement. Cats with hemolymphatic disease are classified as having SMCD (or mast cell leukemia) because the bone marrow, spleen, liver, and blood are commonly involved. Most cats initially have nonspecific signs such as anorexia and vomiting; abdominal distention caused by massive splenomegaly is a consistent feature. As in dogs, the hematologic abnormalities in cats with SMCD are extremely variable and include cytopenias, mastocythemia, basophilia, eosinophilia, or a combination of these; however, a high percentage of cats may have normal CBCs. Cats with the intestinal form of SMCD usually are evaluated because of gastrointestinal signs such as anorexia, vomiting, or diarrhea. Abdominal masses are palpated in approximately one half of these cats. Most tumors involve the small intestine, where they can be solitary or multiple. Metastatic disease affecting the mesenteric lymph nodes, liver, spleen, and lungs is commonly found at the time of presentation. Multiple intestinal masses in cats are most commonly associated with lymphoma and with MCT, although both neoplasms can co-exist. Gastrointestinal tract ulceration has also been documented in affected cats.

Cats with cutaneous MCTs usually initially have solitary or multiple, small (2 to 15 mm), white to pink dermoepidermal masses primarily in the head and neck regions, although solitary dermoepidermal or subcutaneous masses also occur

in other locations. It has been reported that, on the basis of the clinical, epidemiologic, and histologic features, MCTs in cats can be classified as either mast cell-type MCTs (common) or histiocytic-type MCTs (rare). Cats with mast cell-type MCTs are usually older than 4 years of age and have solitary dermal masses; there is no apparent breed predilection. Cats with histiocytic-type MCTs are primarily Siamese cats younger than 4 years of age. Typically, such cats have multiple (miliary) subcutaneous masses that exhibit a benign biologic behavior. Some of these neoplasms appear to regress spontaneously. We have never seen the histiocytic type of disease in cats treated at our clinic, even in Siamese cats with multiple dermoepidermal nodules. The subcutaneous MCTs commonly seen in dogs are extremely rare in cats. Unlike the situation in dogs, the histopathologic grade does not appear to correlate well with the biologic behavior of MCTs in cats (Molander-McCrary et al., 1998).

#### **Diagnosis and Treatment**

The diagnostic approach to cats with MCT is similar to that in dogs. As in dogs, some mast cells in cats are poorly granulated and the granules may not be easily identified during a routine cytologic or histopathologic evaluation.

The treatment for cats with MCTs is controversial. As a general rule, surgery is indicated for cats with a solitary cutaneous mass, for cats with two to five skin masses, and for cats with intestinal or splenic involvement. As discussed previously, cutaneous MCTs in cats are less aggressive than in dogs, and in most affected cats removal of a solitary dermoepidermal MCT using a biopsy punch is curative; the same applies to cats with fewer than five dermoepidermal MCTs. The combination of splenectomy, prednisone, and chloramibucid (Leukeran) treatment is recommended for cats with SMCD, in which survival times in excess of approximately 1 year are common; splenectomy alone does not result in prolonged survival. Surgical excision and prednisone treatment are recommended for cats with intestinal MCT. Prednisone alone (4 to 8 mg/kg by mouth q24-48h) may also be beneficial for cats with systemic or metastatic MCTs. Cats with multiple skin MCTs are best treated with prednisone, in the dosage just given. Although radiotherapy is as effective in cats as in dogs, it is rarely necessary in cats with this neoplasm. When an additional chemotherapeutic agent is needed in cats with MCTs, I usually use chlorambucil (Leukeran, 20 mg/m² by mouth q2 weeks); this drug seems to be quite effective and well tolerated. In my limited experience, lomustine (CCNU) is not very effective in cats with MCTs.

#### INJECTION SITE SARCOMAS IN CATS

An association between injections/vaccination and the development of sarcomas has been recently recognized in cats, and epidemiologic studies have confirmed the association. In this syndrome fibriosarcomas (FSAs) or occasionally other types of sarcomas develop in the subcutis

or muscle in the interscapular region or the thigh, common sites of injection/vaccination. It is estimated that a sarcoma develops in one to two of 10,000 cats that receive an injection. Although the exact pathogenesis is still unclear, both the adjuvants and the local immune response against the antigens (i.e.; inflammation) have been implicated as causative agents.

A rapidly growing soft tissue mass develops in the region weeks to months after vaccination or injection in cats with injection site sarcomas (ISSs). A vaccine- or injection-associated inflammatory reaction may precede the development of this neoplasm. Therefore an ISS should be suspected in any cat with a superficial or deep mass in the interscapular or thigh regions, and every effort should be made to establish a diagnosis immediately. Although FNA findings may provide a definitive answer, more often a surgical biopsy is necessary because sarcomas do not consistently exfoliate cells (see Chapter 75).

Although most FSAs in dogs and cats have a low metastatic potential, ISSs are quite aggressive and should be treated accordingly. Although studies are currently in progress, on the basis of the results of studies reported in the literature and on the findings in cats seen at our clinic, the rate of metastasis of ISSs is high (probably as high as 50% to 70%). Pulmonary metastatic lesions can be detected at presentation in a high proportion of cats; we have also seen ocular metastases as the main presenting feature in a few cats with ISSs.

The treatment of choice for cats with ISS is aggressive surgical excision (see Chapter 76). In keeping with the maxim "cut it once, but cut it all," an en bloc resection (to include any biopsy tracts) should be performed immediately after the diagnosis is established, provided there is no metastatic disease. In a recent study cats treated with aggressive surgery had significantly longer disease-free survival times than cats treated with conservative surgery (274 versus 66 days); also, cats with tumors in the limbs had significantly longer diseasefree survival times than cats with tumors in the trunk (325 versus 66 days; Hershey et al., 2000). Complete surgical excision of a relatively small ISS (i.e., <2 cm in diameter) is usually associated with long-term remissions. Although the role of postoperative adjuvant chemotherapy has not been thoroughly evaluated, cats with large or incompletely excised tumors may benefit from treatment with mitoxantrone and cyclophosphamide, doxorubicin and cyclophosphamide, or carboplatin. We have seen objective complete or partial responses in cats with nonresectable or metastatic ISS treated with doxorubicin/ cyclophosphamide combinations or with carboplatin alone; some of these cats have been in remission for longer than 1 year. If metastatic disease is already present, chemotherapy is not usually effective.

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#### Cancer Chemotherapy Protocols Commonly Used at the l Ohio State University Veterinary Teaching Hospital

#### 1. Lymphoma

A. Induction of remission

1. COAP protocol

Cyclophosphamide: 50 mg/m² PO q48h for 8 weeks in dogs; 200-300 mg/m² PO q3 weeks in cats

Vincristine: 0.5 mg/m<sup>2</sup> IV once per week for 8 weeks

Cytosine arabinoside: 100 mg/m² IV or SC divided q12h for 4 days

Prednisone: 40-50 mg/m² PO q24h for 1 week; then 20-25 mg/m² PO q48h for 7 weeks

In cats cystosine arabinoside is administered for only 2 days and the remaining three drugs (cyclophosphamide, vincristine, prednisone) are administered for 6 weeks rather than 8 weeks.

<sup>\*</sup> The daily dose should be divided into two to four daily administrations.

<sup>\*</sup> The duration of chemotherapy using this protocol varies.

PO, Orally; IV, intravenously; SC, subcutaneously; IM, intramuscularly; CRI, constant rate infusion.

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#### Cancer Chemotherapy Protocols Commonly Used at the Ohio State University Veterinary Teaching Hospital—cont'd

2. COP protocol

Cyclophosphamide: 50 mg/m<sup>2</sup> PO q48h or 300 mg/m<sup>2</sup> PO q3 weeks\*

Vincristine: 0.5 mg/m<sup>2</sup> IV once per week

Prednisone: 40-50 mg/m<sup>2</sup> PO q24h for 1 week; then 20-25 mg/m<sup>2</sup> PO q48h

3. CLOP protocol

As in COP protocol but with the addition of Lasparaginase at a dosage of 10,000-20,000 IU/m² IM q4-6 wk

4. CHOP protocol (21-day cycle)

Cyclophosphamide:  $200-300 \text{ mg/m}^2 \text{ PO}$  on day  $10 \text{ Doxorubicin: } 30 \text{ mg/m}^2 \text{ IV or } 1 \text{ mg/kg if } < 10 \text{ kg on day } 1$ 

Vincristine: 0.75 mg/m<sup>2</sup> IV on days 8 and 15

Prednisone: 40-50 mg/m<sup>2</sup> PO q24h on days 1-7; then 20-25 mg/m<sup>2</sup> PO q48h on days 8-21

Sulfa-trimethoprim: 15 mg/kg PO g12h

5. UW-19 protocol (This protocol uses no maintenance chemotherapy—for additional information please see text)

Week 1: Vincristine: 0.5-0.75 mg/m², IV L-asparaginase: 400 IU/KG IM or SC Prednisone: 2 mg/kg PO q24h

Week 2: Cyclophosphamide: 200-250 mg/m², IV

Prednisone: 1.5 mg/kg PO q24h

Week 3: Vincristine: 0.5-0.75 mg/m², IV Prednisone: 1 mg/kg PO q24h

Week 4: Doxorubicin: 30 mg/m² (or 1 mg/kg if <10 kg) IV

Prednisone: 0.5 mg/kg PO q24h

Week 5: No treatment

Week 6: Vincristine: 0.5-0.75 mg/m<sup>2</sup>, IV

Week 7: Cyclophosphamide: 200-250 mg/m², IV

Week 8: Vincristine: 0.5-0.75 mg/m², IV

Week 9: Doxorubicin: 30 mg/m² (or 1 mg/kg if <10 kg) IV

Week 10: No treatment

Week 11: Vincristine: 0.5-0.75 mg/m<sup>2</sup>, IV

Week 12: Cyclophosphamide: 200-250 mg/m², IV

Week 13: Vincristine: 0.5-0.75 mg/m<sup>2</sup>, IV

Week 14: Doxorubicin: 30 mg/m<sup>2</sup> (or 1 mg/kg if <10 kg) IV

Week 15: No treatment

Week 16: Vincristine: 0.5-0.75 mg/m<sup>2</sup>, IV

Week 17: Cyclophosphamide: 200-250 mg/m<sup>2</sup>, IV

Week 18: Vincristine: 0.5-0.75 mg/m², IV

Week 19: Doxorubicin: 30 mg/m<sup>2</sup> (or 1 mg/kg if <10 kg) IV

#### B. Maintenance

1. LMP protocol

Chlorambucil: 20 mg/m<sup>2</sup> PO every other week

Prednisone: 20-25 mg/m<sup>2</sup> PO q48h

Methotrexate: 2.5-5 mg/m<sup>2</sup> PO 2 or 3 times per week

2. LAP protocol

Chlorambucil: 20 mg/m² PO every other week

Prednisone: 20-25 mg/m<sup>2</sup> PO q48h

Cytosine arabinoside (Cytosar): 200-400 mg/m<sup>2</sup> SC q2 weeks; alternating with chlorambucil

3. COP protocol used every other week for 6 cycles; then every third week for 6 cycles; then monthly thereafter

#### C. "Rescue" DOGS

1. D-MAC protocol (repeat continuously for 10-16 weeks)

Dexamethasone: 0.5 mg/lb (0.23 mg/kg) PO or SC on days 1 and 8

Actinomycin D (Cosmegen): 0.75 mg/m² IV push on day 1

Cytosine arabinoside (Cytosar): 200-300 mg/m² IV drip over 4 hours or SC on day 1

Melphalan (Alkeran): 20 mg/m<sup>2</sup> PO on day 8 (after 4 doses of melphalan, substitute Leukeran at the same dose)

2. CHOP protocol if second relapse in response to COAP protocol or if good response to Adriamycin was previously observed



#### Cancer Chemotherapy Protocols Commonly Used at the Ohio State University Veterinary Teaching Hospital—cont'd

#### **CATS**

1. ACD protocol (21-day cycle)

Doxorubicin: 1 mg/kg IV on day 1

Cyclophosphamide: 200-300 mg/m<sup>2</sup>, PO, on day 10

Dexamethasone: 4 mg/cat, PO q1-2 weeks

AMD protocol

Cytosine arabinoside: 100-200 mg/m²/day IV drip for 1-2 days Mitoxantrone: 4 mg/m<sup>2</sup> in IV drip, mixed in the bag with the Cytosar

Dexamethasone: 0.5-1 mg/lb (0.23-0.45 mg/kg) PO weekly; repeat q3 weeks

II. Acute lymphoid leukemia (ALL)

COAP, CLOP, or COP protocols

III. Chronic lymphocytic leukemia (CLL)

1. Chlorambucil: 20 mg/m² PO q2 weeks (with or without prednisone, 20 mg/m² PO q48h)

2. Cyclophosphamide: 50 ma/m<sup>2</sup> PO a48h

Prednisone: 20 mg/m<sup>2</sup> PO g48h

IV. Acute myelogenous leukemia

1. Cytosine arabinoside: 5-10 mg/m<sup>2</sup> SC q12h for 2-3 weeks; then on alternate weeks

2. Cytosine arabinoside: 100-200 mg/m<sup>2</sup> in IV drip over 4 hours

Mitoxantrone: 4-6 mg/m² in IV drip over 4 hours; repeat every 3 weeks

V. Chronic myelogenous leukemia

1. Hydroxyurea (Hydrea): 50 mg/kg PO q24-48h until normal white blood count

VI. Multiple myeloma

1. Melphalan (Alkeran): 2-4 mg/m² PO g24h for 1 week; then g48h. Can also be given at 6-8 mg/m² PO for 5 days, repeating every 21 days

Prednisone: 40-50 mg/m<sup>2</sup> PO q24h for 1 week, then 20 mg/m<sup>2</sup> PO q48h

2. As in III.2

VII. Mast cell tumors (systemic)

1. Prednisone: 40-50 mg/m<sup>2</sup> PO g24h for 1 week; then 20-25 mg/m<sup>2</sup> PO g48h

2. Lomustine (CCNU): 60- mg/m<sup>2</sup> PO g3 wks (with or without prednisone as in 1)

3. LVP protocol

Vinblastine (Velban): 2 mg/m<sup>2</sup> IV q6 weeks alternating with

Lomustine (CCNU): 60 mg/m<sup>2</sup> PO q6 weeks

Prednisone: 20-25 mg/m<sup>2</sup> PO q48h

VIII. Soft-tissue sarcomas—dogs

1. VAC protocol (21-day cycle)

Vincristine: 0.75 mg/m<sup>2</sup> IV on days 8 and 15

Doxorubicin: 30 mg/m<sup>2</sup> IV (or 1 mg/kg if <10 kg) on day 1

Cyclophosphamide: 200-300 mg/m² PO on day 10

Sulfa-trimethoprim: 15 mg/kg PO q12h

IX. Soft-tissue sarcomas—cats

1. AC protocol (21 day cycle)

Doxorubicin: 1 mg/kg IV on day 1

Cyclophosphamide: 200-300 mg/m<sup>2</sup> on day 10

2. VAC protocol (28-day cycle)

Vincristine: 0.5 mg/m<sup>2</sup> IV on days 8, 15, and 22

Doxorubicin: 1 mg/kg IV on day 1

Cyclophosphamide: 200-300 mg/m<sup>2</sup> on day 10

3. MiC protocol (21-day cycle)

Mitoxantrone: 4-6 mg/m<sup>2</sup> in IV drip over 4 hours on day 1 Cyclophosphamide: 200-300 mg/m² PO on day 10

4. Carboplatin: 200-280 mg/m<sup>2</sup> IV q3 weeks

X. Osteosarcoma-dogs

1. Doxorubicin: 30 mg/m<sup>2</sup> IV q2 weeks for 5 doses

2. Carboplatin: 300 mg/m<sup>2</sup> IV a3 weeks for 4-6 doses

Doxorubicin and carboplatin as above, alternating drugs q3 weeks for 2-3 doses each

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#### Cancer Chemotherapy Protocols Commonly Used at the Ohio State University Veterinary Teaching Hospital—cont'd

#### XI. Carcinomas—dogs

1. FAC protocol

5-Fluorouracil: 150 mg/m<sup>2</sup> IV on days 8 and 15

Doxorubicin: 30 mg/m<sup>2</sup> (or 1 mg/kg if <10 kg) IV on day 1

Cyclophosphamide: 200-300 mg/m<sup>2</sup> PO on day 10

Sulfa-trimethoprim: 15 mg/kg PO q12h

2. VAF protocol

Vincristine: 0.75 mg/m<sup>2</sup> IV on days 8 and 15

Doxorubicin: 30 mg/m² (or 1 mg/kg if <10 kg) IV on day 1

5-Fluorouracil:  $150 \text{ mg/m}^2$  IV on days 1, 8, and 15

3. VAC protocol

4. Carboplatin: 300 mg/m<sup>2</sup> IV q3 weeks

5. Gemcitabine: 675 mg/m<sup>2</sup>, IV CRI for 30 minutes, q2 weeks

#### XII. Carcinomas—cats

## 5-Fluorouracil is toxic for the cat, producing severe, and often fatal, central nervous system signs. Cisplatin is also extremely toxic, causing acute pulmonary toxicity in this species.

1. Carboplatin: 200-280 mg/m<sup>2</sup> IV q3 weeks

2. AC protocol (21-day cycle)

Doxorubicin: 1 mg/kg IV on day 1

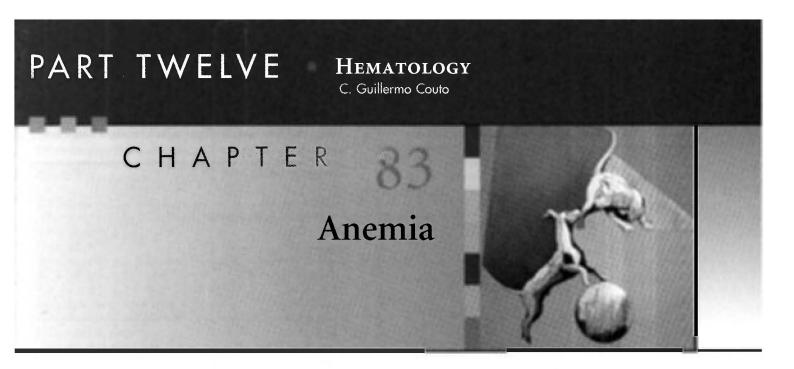
Cyclophosphamide: 200-300 mg/m<sup>2</sup> PO on day 10

3. MiC protocol (21-day cycle)

Mitoxantrone: 4-6 mg/m² IV drip over 4 hours on day 1 Cyclophosphamide: 200-300 mg/m² PO on day 10

4. MiCO protocol (21-day cycle)

Mitoxantrone: 4-6 mg/m² IV drip over 4 hours on day 1 Cyclophosphamide: 200-300 mg/m² PO on day 10 Vincristine: 0.5-0.6 mg/m² IV on days 8 and 15



#### CHAPTER OUTLINE

DEFINITION
CLINICAL AND CLINICOPATHOLOGIC EVALUATION
PRINCIPLES OF MANAGEMENT OF THE ANEMIC
PATIENT

REGENERATIVE ANEMIAS

Blood Loss Anemia Hemolytic Anemia

NONREGENERATIVE ANEMIAS

Anemia of Chronic Disease

Bone Marrow Disorders

Anemia of Renal Disease

Acute and Peracute Blood Loss or Hemolysis (First 48 to 96 Hours)

SEMIREGENERATIVE ANEMIAS

Iron Deficiency Anemia

PRINCIPLES OF TRANSFUSION THERAPY

**Blood Groups** 

Cross-Matching and Blood Typing

Blood Administration

Complications of Transfusion Therapy

#### **DEFINITION**

Anemia is defined as a decrease in the red blood cell (RBC) mass. In practical terms it can be defined as a decrease in the packed cell volume (PCV) or hematocrit (HCT), the hemoglobin (Hb) concentration, or the RBC count below reference values for the species. In the context of this chapter, PCV and HCT are used interchangeably. In special circumstances, anemia is diagnosed in a given patient with a HCT that has decreased over time even though it may remain within reference values. For example, Greyhounds rarely

have HCT values less than 50%, so an anemic Greyhound may have a HCT within the reference range for the dog. Because the reference values reflect the actual status in 95% of the feline and canine population, occasionally an "abnormal" value is indeed normal for a particular animal, prompting a needless evaluation in search of other abnormalities. Of note, anemia does not constitute a primary diagnosis; therefore every effort should be made to identify its cause.

## CLINICAL AND CLINICOPATHOLOGIC EVALUATION

When interpreting the HCT, Hb concentration, or RBC count, the clinician should keep in mind that in some situations these values are above (e.g., sight hounds) or below (e.g., puppyhood, pregnancy) the reference value for the species. From a practical standpoint, when evaluating the erythroid series, the clinician does not need to assess all the values in the complete blood count (CBC) because several of them provide identical information. For example, the HCT, Hb concentration, and RBC count provide the same type of information (i.e., an increase in the number of RBCs usually results in an increased HCT and Hb concentration, and vice versa). Thus when evaluating the erythron in a CBC, the HCT is typically used as an indirect index of the RBC mass (or number).

The main clinical manifestations of anemia in cats and dogs include pale or icteric mucous membranes, lethargy, exercise intolerance, pica (mainly in cats), and decreased overall activity (Box 83-1). These clinical signs can be acute or chronic and can vary in severity; the duration of the clinical signs may not reflect the mechanism of anemia. For example, "acute" clinical signs are common in cats with chronic anemia; most cats with chronic anemia compensate by shifting the oxyhemoglobin dissociation curve to the right, thus releasing oxygen to the tissues more readily.



BOX 83-1

Clinical Manifestations of Anemia in Cats and Dogs

#### History

- 1. Family history
- 2. Exercise intolerance, syncopal episodes
- 3. Pallor, jaundice
- 4. Localized or generalized bleeding
- 5. FeLV or FIV infection
- 6. Malnutrition, malabsorption
- 7. Chronic inflammation, cancer
- 8. Travel history

#### **Physical Examination**

- 1. Pallor, jaundice, petechiae, ecchymoses
- 2. Lymphadenopathy
- 3. Hepatomegaly, splenomegaly
- Tachycardia, heart murmur, cardiomegaly, left ventricular hypertrophy
- 5. Occult blood in the stool
- 6. Hematuria

FeLV, Feline leukemia virus; FIV, feline immunodeficiency virus.

Therefore cats are clinically stable until their HCT level gets below a specific percent and they develop "acute" signs. Owners may also detect some of the adaptive changes to anemia, such as tachycardia or an increased precordial beat. Following are several important questions to ask the owner of an anemic cat or dog:

- Is the pet currently receiving any medication? Certain drugs can cause hemolysis, gastrointestinal blood loss, or bone marrow hypoplasia.
- Have the owners detected any blood loss or dark (tarry) stool? Gastrointestinal tract bleeding from a gastric ulcer or a tumor can lead to iron deficiency anemia (IDA).
- Have the owners noticed any fleas? Severe flea infestation can cause IDA.
- Has the cat recently been tested for feline leukemia (FeLV)
  or feline immunodeficiency virus (FIV) infections? Retroviruses can cause bone marrow hypoplasia, myelodysplasia, or leukemias, leading to cytopenias.
- Has the owner noticed any ticks on the dog? Ehrlichiosis can cause bone marrow hypoplasia; babesiosis can cause hemolysis.
- Has the pet been vaccinated recently? Modified live vaccines can cause bleeding as a result of platelet dysfunction or thrombocytopenia, or they can be associated with immune-mediated hemolysis.
- Has the bitch received any "shots" for mismating recently?
   Estrogen derivatives can cause bone marrow aplasia or hypoplasia.

In addition to these questions, a detailed travel and pharmacologic history should be obtained. Certain infectious



BOX 83-2

Drugs and Toxins Associated with Anemia in Cats and Dogs

Acetaminophen

Antiarrhythmics

Anticonvulsants

Antiinflammatories (nonsteroidal)

**Barbiturates** 

Benzocaine

Chemotherapeutic agents

Chloramphenicol

Cimetidine

Gold salts

Griseofulvin

Levamisole

Methimazole

Methionine

Methylene blue

Metronidazole

Penicillins and cephalosporins

**Phenothiazines** 

Propylthiouracil

Propylene glycol

Sulfa derivatives

Vitamin K

Zinc

diseases associated with anemia may have geographic distribution (e.g., babesiosis in the southeastern part of the United States); however, because dogs frequently travel throughout the United States, the geographic disease distribution is becoming less common. Some drugs and toxins that have been associated with anemia in cats and dogs are listed in Box 83-2.

When evaluating a patient with pallor, determine whether it is attributable to hypoperfusion or anemia (i.e., not every patient with pale mucous membranes is anemic). The simplest approach is to evaluate the HCT and the capillary refill time (CRT). Dogs and cats with cardiovascular disease and hypoperfusion usually have normal HCT values and additional clinical signs, whereas symptomatic anemic dogs have low HCT. Dogs and cats with congestive heart failure occasionally have dilutional anemia caused by intravascular fluid retention. The CRT may be difficult to evaluate in anemic cats and dogs because of the absence of contrast from the pallor.

The clinician should also look for petechiae, ecchymoses, and evidence of deep bleeding in animals with pallor. These findings are suggestive of a platelet or clotting factor deficiency (as seen in animals with Evans syndrome, disseminated intravascular coagulation [DIC], or acute leukemias; see Chapter 87), resulting in bleeding and secondary anemia. Particular attention should be paid to the lymphoreticular organs, such as the lymph nodes and spleen, because several disorders associated with anemia may also result in lymphadenopathy, hepatosplenomegaly, or both (Table 83-1).



Disorders Commonly Associated with Anemia and Hepatomegaly, Splenomegaly, and/or Lymphadenopathy

DISORDER	FREQUENCY	SPECIES
lumnhama	c	D, C
Lymphoma	<u></u>	
Mycoplasmosis	F	C > D
Acute leukemias	F	C, D
Ehrlichiosis	F*	D > C
Systemic mast cell disease	R	C > D
Bone marrow hypoplasia	R	C, D
1HA	F	D > C
Hypersplenism	R	D, C

<sup>\*</sup>Geographic variation.

Abdominal radiographs in a dog with intravascular hemolysis may show metallic foreign bodies in the stomach, a potential source of zinc that frequently results in RBC lysis.

The degree of anemia may be helpful in establishing its cause. To this end, anemias are graded according to HCT level as follows:

	Dogs	Cats
Mild	30%-36%	20%-24%
Moderate	18%-29%	15%-19%
Severe	<18%	<14%

For example, if an anemic dog or cat has severe anemia, certain causes (e.g., bleeding, anemia of chronic disease, anemia of renal disease, IDA) can immediately be ruled out because none of those mechanisms is likely to result in such a severe decrease in the HCT; therefore the patient most likely has hemolysis or a bone marrow disorder (see below). The severity of the clinical signs usually also correlates with the pathogenesis of the anemia. For example, a dog or cat with severe anemia and mild to moderate clinical signs more likely has a chronic cause of anemia (e.g., bone marrow disease); acute causes of severe anemia (e.g., hemolysis) result in clinical signs of marked severity because the adaptive compensatory changes have not yet occurred.

As part of the evaluation of a patient's HCT, the plasma should be examined for evidence of icterus or hemolysis and the protein content should be determined with a refractometer. The microhematocrit tube should be carefully inspected for evidence of autoagglutination (see p. 1215) and a slide agglutination test should be performed (see below). A blood smear should be evaluated to detect morphologic changes that may point the clinician toward the cause of the anemia.

A common issue that comes up often is whether a general practicing veterinarian should do CBCs in-house or send them to a referral laboratory. The recent introduction of accurate, user-friendly, benchtop hematology analyzers has



BOX 83-3

Pathogenetic Classification of Anemias

Regenerative	
Blood loss (after 48-96 hours) Hemolysis	
Semiregenerative	
IDA	
Nonregenerative	
ACD	
ARD	
Bone marrow disorder	
Blood loss/hemolysis (first 48-96 hours)	
Endocrine anemia	

IDA, Iron deficiency anemia; ACD, anemia of chronic disease; ARD, anemia of renal disease.

revolutionized the practice of small animal hematology. Most of these instruments are trouble free and provide accurate results. However, when values are outside the reference range or are flagged, the clinician or technician should evaluate a blood smear from the patient in question.

Once the patient has been established as anemic, it should be determined whether the anemia is regenerative or nonregenerative. This is accomplished by obtaining a reticulocyte count during a routine CBC (some of the in-house analyzers, such as the LaserCyte from IDEXX Laboratories, Westbrook, Maine, provide reticulocyte counts) or by evaluating a blood smear for the presence of polychromasia. This reflects the pathogenesis of the anemia, thereby dictating the most logical diagnostic and therapeutic approach (Box 83-3).

In brief, regenerative anemias always stem from extramarrow causes because the presence of reticulocytes or polychromatophilic RBCs (i.e., immature RBCs) in the circulation is a clear indication of a functional bone marrow. Regenerative anemias can result only from hemolysis or blood loss. Nonregenerative anemias can be caused by bone marrow or extra-marrow disorders, such as erythroid hypoproliferation, chronic inflammatory disease, chronic kidney disease, and acute hemorrhage or hemolysis (first 48 to 96 hours). Although IDA is traditionally classified as nonregenerative, most dogs with chronic blood loss leading to iron deficiency display a mild to moderate degree of regeneration, and the RBC indices are different than in other nonregenerative anemias (see below). Therefore I prefer to classify IDA in a separate category. Regenerative anemias are usually acute, whereas nonregenerative anemias are either peracute (i.e., blood loss or hemolysis of less than 48 hours' duration) or, more often, chronic.

During the initial clinical evaluation of an anemic patient, examination of the blood smear usually suffices in determining whether the bone marrow is responding appropriately to the anemia (i.e., whether the anemia is regenerative or not).

F, Frequent; R, rare; D, dog; C, cat.



Interpretation of Morphologic RBC Abnormalities in Cats and Dogs

#### MORPHOLOGIC ABNORMALITY COMMONLY ASSOCIATED DISORDERS

Macrocytosis Regeneration, breed-related characteristic (Poodles); FeLV or FIV infection;

dyserythropoiesis (bone marrow disease)

Microcytosis Iron deficiency; breed-related characteristic (Akita, Sharpei, Shiba Inu); portosystemic

shunt; polycythemia (erythrocytosis)

Hypochromasia Iron deficiency Polychromasia Regeneration

Poikilocytosis Regeneration; iron deficiency; hyposplenism

Schistocytosis (fragments)

Spherocytosis

Acanthocytosis (spur cells)

Microangiopathy; hemangiosarcoma; DIC; hyposplenism

IHA; mononuclear phagocytic neoplasm; zinc toxicity

Hemangiosarcoma; liver disease; hyposplenism

Echinocytosis (burr cells)

Artifact; renal disease; pyruvate kinase deficiency anemia

Elliptocytosis Congenital elliptocytosis (dogs)
Heinz bodies Oxidative insult to RBCs
Howell-Jolly bodies Regeneration; hyposplenism

Autoagglutination IH

Metarubricytosis Breed-related characteristic (Schnauzer, Dachshund); extramedullary hematopoiesis;

regeneration; lead toxicity; hemangiosarcoma

Leukopenia See text Thrombocytopenia See text

Pancytopenia Bone marrow disorder; hypersplenism

Modified from Couto CG et al: Hematologic and oncologic emergencies. In Murtaugh R et al, editors: Veterinary emergency and critical care medicine, St Louis, 1992, Mosby.

RBC, Red blood cell; FeLV, feline leukemia virus; FIV, feline immunodeficiency virus; DIC, disseminated intravascular coagulation; IHA, immune hemolytic anemia.

Several pieces of information can be acquired during the examination of a good-quality, properly stained blood smear, including the RBC size and morphology, the presence of autoagglutination, the approximate numbers and morphology of white blood cells and platelets, the presence of nucleated RBCs, the presence of polychromasia (indicative of regeneration), and the presence of RBC parasites. The clinician should perform this cursory evaluation of the blood smear; a blood sample should be submitted to a diagnostic laboratory for further analysis and evaluation by a clinical pathologist if the diagnosis is still uncertain after evaluating the blood smear. Some of the abnormalities detected during a careful examination of the blood smear and their clinical implications are summarized in Table 83-2. This evaluation should be conducted under oil immersion lens in a monolayer field, in which the erythrocytes are in a single layer and 50% of the cells are touching.

A CBC and a reticulocyte count in an anemic patient provide more absolute data by which to assess the degree of regeneration. However, the information presented below must be used cautiously because the number of reticulocytes should increase proportionally to the decrease in the HCT. For example, a reticulocyte count of  $120,000/\mu L$  or 4% represents an appropriate response for a dog with an HCT of 30% but not for one with an HCT of 10%. The following points generally hold true:

- If the RBC indices are macrocytic and hypochromic, the anemia is most likely associated with the presence of high numbers of reticulocytes (which are larger and contain less Hb than mature RBCs); therefore the anemia is likely regenerative.
- If the reticulocyte count is more than 120,000/μL or 4% and the anemia is mild to moderate, the anemia is likely regenerative.

As part of the evaluation of a patient with regenerative anemia, it is beneficial to determine the serum or plasma protein concentration because blood loss usually results in hypoproteinemia and hemolysis does not. Other physical examination and clinicopathologic findings that help distinguish blood loss from hemolytic anemias are listed in Table 83-3.

## PRINCIPLES OF MANAGEMENT OF THE ANEMIC PATIENT

The first basic principle of the management of anemic (or bleeding) patients is to collect *all* blood samples before instituting any therapy. Because the condition in most of these patients may constitute a true emergency at the time of presentation, samples often are not collected until the patient



#### Criteria for Differentiating Blood Loss from Hemolytic Anemias

VARIABLE	BLOOD LOSS	HEMOLYSIS	
Serum (plasma) protein concentration	Normal-low	Normal-high	
Evidence of bleeding	Common	Rare	
Icterus	No	Common	
Hemoglobinemia	No	Common	
Spherocytosis	No	Common	
Hemosiderinuria	No	Yes	
Autoagglutination	No	Occasional	
Direct Coombs test	Negative	Usually positive (in IHA)	
Splenomegaly	No	Common	
RBC changes	No	Common (see Table 83-2)	

Reprinted from Couto CG et al: Hematologic and oncologic emergencies. In Murtaugh R et al, editors: Veterinary emergency and critical care medicine, St Louis, 1992, Mosby.

IHA, Immune hemolytic anemia; RBC, red blood cell.

has been completely stabilized, resulting in treatmentinduced changes in hematologic or serum biochemical values.

As a general rule, because of the acute onset of these disorders, patients with regenerative anemias (i.e., blood loss or hemolysis) require more aggressive therapy than those with nonregenerative forms. Specific therapy should be instituted once the clinician has determined that the patient's condition is stable and whether or not the anemia is regenerative. The diagnosis and management of different forms of anemia in cats and dogs are discussed throughout the remainder of this chapter.

#### REGENERATIVE ANEMIAS

#### **BLOOD LOSS ANEMIA**

Acute blood loss in otherwise normal dogs and cats results in reticulocytosis (i.e., regeneration) within 48 to 96 hours. Therefore animals evaluated shortly after a traumatic injury and severe blood loss usually have nonregenerative anemias with low-to-normal serum (plasma) protein concentrations. The source of bleeding should be identified and the bleeding stopped; if the patient is bleeding as a result of a systemic hemostatic defect, it should be identified and specific treatment should be initiated (see Chapter 87). Aggressive intravenous (IV) fluid therapy with crystalloids or colloids or the transfusion of blood or blood products is often required in patients with anemia caused by acute blood loss.

#### **HEMOLYTIC ANEMIA**

In human beings the bone marrow is capable of undergoing hyperplasia until its production rate is increased approximately sixfold to eightfold; the same is probably true for dogs and cats. As a consequence, a considerable number of RBCs must be destroyed before anemia develops. As is the case in cats and dogs with blood loss anemia, patients with peracute

hemolysis can be in a nonregenerative state at the time of presentation because the bone marrow has not yet been able to mount a regenerative response. In addition, in some dogs with immune-mediated hemolysis, the destruction of erythroid precursors in the bone marrow results in a lack of regeneration.

On the basis of their pathogenesis, hemolytic anemias can be classified as extravascular (i.e., the RBCs are destroyed by the mononuclear phagocytic cells) or intravascular (i.e., the RBCs are lysed by antibody-complement, drugs, toxins, or by hitting fibrin strands). On the basis of the age of the animal at onset, anemias can be classified as congenital or acquired (Table 83-4). Most dogs and cats with hemolytic anemia seen at my clinic have acquired extravascular hemolysis.

In extravascular hemolysis, RBCs are phagocytosed by the mononuclear-phagocytic system (MPS) in the spleen, liver, and bone marrow. Stimuli that trigger RBC phagocytosis consist mainly of intracellular inclusions, such as RBC parasites or Heinz bodies (the latter are commonly seen in cats) and membrane coating with immunoglobulin (Ig) G or M (common in dogs). Congenital RBC enzymopathies can also precipitate extravascular hemolysis. Once abnormal RBCs are recognized, the MPS rapidly phagocytoses them, resulting in a decrease in the number of circulating RBCs and the generation of cells with specific morphologic changes (e.g., spherocytes). Anemia develops if the destruction of RBCs continues. Spherocytes are RBC "leftovers," in that after a mononuclear-phagocytic cell takes a "bite" of cytoplasm and membrane, the membrane is resealed; the RBC then loses its redundant membrane and consequently its central pallor. Spherocytes are characteristic of immune hemolytic anemia (IHA), although they can occasionally be seen in other disorders, such as Babesia gibsoni infection or zinc toxicity. Immune hemolysis is the most common cause of extravascular hemolytic anemia in dogs at my hospital. Drugassociated hemolysis (e.g., \beta-lactam antibiotics) and



Causes of Hemolytic Anemia in Dogs and Cats

DISORDER	SPECIES	BREED		
Congenital (Inherited?)				
Pyruvate kinase deficiency	D, C	Basenji, Beagle, West Highland White Terrier, Cairn Terrier, Poodle, Dachshund, Chihuahua, Pug, American Eskimo, Abyssinian, Somali, domestic short-haired cat		
PFK deficiency	D	English Springer Spaniel, Cocker Spaniel		
Stomatocytosis	D	Alaskan Malamute, Miniature Schnauzer		
Nonspherocytic hemolytic anemia	Đ	Poodle, Beagle		
Acquired				
IHA	D > C	All		
Neonatal isoerythrolysis	С	British breeds, Abyssinian, Somali (other type B cats)		
Microangiopathic hemolytic anemia	D > C	All		
Infectious				
Mycoplasmosis	C > D	All		
Babesiosis	D > C	All		
Cytauxzoonosis	С	All		
Ehrlichiosis	D > C	All		
Hypophosphatemia	D, C	All		
Oxidants				
Acetaminophen	С	All		
Phenothiazines	D, C	All		
Benzocaine	С	All		
Vitamin K	D, C	All		
Methylene blue	C > D	All		
Methionine	C C	All		
Propylene glycol	С	All		
Drugs that Can Cause Immune Hemolysi	s			
Sulfas	D > C	Doberman, Labrador Retriever		
Anticonvulsants	D	All		
Penicillins and cephalosporins	D > C	All		
Propylthiouracil	C C	All		
Methimazole	Ç	All		
Antiarrhythmics?	D	All		
Zinc	D	All		

Modified from Couto CG et al: Hematologic and oncologic emergencies. In Murtaugh R et al, editors: Veterinary emergency and critical care medicine, St Louis, 1992, Mosby.

PFK, Phosphofructokinase; IHA, immune hemalytic anemia.

mycoplasmosis (formerly known as haemobartonellosis) are the two most common causes in cats, although IHA is now more common in this species. Other causes of extravascular hemolytic anemia in dogs and cats are listed in Table 83-4.

Intravascular hemolysis can occur as a consequence of direct RBC lysis caused by antibodies that activate complement (e.g., immune-mediated hemolysis), infectious agents (e.g., Babesia canis infection), drugs or toxins (e.g., zinc in pennies minted after 1983, in pet carrier bolts, other hardware, and zinc oxide-containing ointments), metabolic imbalances (e.g., hypophosphatemia in dogs and cats with diabetes mellitus treated with insulin), or increased shearing

of RBCs (e.g., microangiopathy, DIC). Intravascular hemolysis is considerably less common in dogs and cats than extravascular hemolysis, with the notable exception of DIC in dogs with hemangiosarcoma, zinc toxicity, and hypophosphatemia. Certain congenital enzymopathies (e.g., phosphofructokinase [PFK] deficiency) in dogs also result in intravascular hemolysis.

Dogs with *congenital* (frequently familial) hemolytic anemias may have relatively prolonged clinical courses at the time of presentation, with the notable exception of English Springer Spaniels with PFK deficiency—induced hemolysis, in which acute hemolytic episodes occur after they hyper-

ventilate during excitement or field work (i.e., alkaline hemolysis). Dogs and cats with acquired hemolytic anemias are usually evaluated because of acute clinical signs consisting of pallor, with or without icterus (in my experience, only approximately half of dogs and a lower percentage of cats with hemolytic anemia are icteric); splenomegaly may be a prominent finding. If the patient has associated thrombocytopenia (e.g., Evans syndrome, DIC), petechiae and ecchymoses may be present. Clinical signs and physical examination findings associated with the primary disease can also be present in cases of secondary hemolytic anemias; however, as opposed to human beings, they are extremely rare in dogs and cats.

In the evaluation of dogs or cats with hemolytic anemia, a careful examination of the blood smear is mandatory. Morphologic abnormalities pathognomonic for or highly suggestive of a particular etiology are often detected with this method (see Table 83-2). The sample should also be tested for autoagglutination; this is done by placing a large drop of anticoagulated blood on a glass slide at room temperature and at 4° C. Agglutination can be distinguished from rouleaux formation by diluting the blood 5:1 or 10:1 in saline solution (this disaggregates rouleaux); rouleaux formation is common in cats but rare in dogs. A direct Coombs test to detect RBC-bound Ig should always be performed in dogs and cats with suspected hemolysis (see below). As a general rule, the presence of Ig coating on the RBCs indicates immune-mediated hemolysis. A positive Coombs test result should be interpreted with caution, however, because certain drugs and hemoparasites can induce formation of antibodies that bind to the RBCs, thus causing secondary immune hemolysis (e.g., cats with mycoplasmosis). The pretreatment of an animal with corticosteroids may also result in decreased binding of Ig molecules to the surface of the RBC, thus resulting in false-negative results. Direct Coombs tests are usually not necessary in animals with autoagglutination because this phenomenon connotes the presence of Ig on the surface of the RBCs (i.e., biologic Coombs test). Cryoagglutination (i.e., the agglutination of RBCs if the blood sample is refrigerated for 6 to 8 hours) occurs in a large proportion of cats with mycoplasmosis and is usually associated with IgM coating on the RBCs.

If an etiologic agent cannot be identified (e.g., RBC parasite, drug, pennies in the stomach), the patient should be treated for primary or idiopathic IHA while further test results (e.g., serologic tests or polymerase chain reaction [PCR] for hemoparasites) are pending. As previously mentioned, primary IHA is considerably more common in dogs than in cats; thus every effort should be made to identify a cause of hemolysis in cats, such as drugs or hemoparasites. A detailed discussion of IHA is presented below.

Hemolytic anemias not associated with immune destruction of the RBCs are treated by removal of the cause (e.g., drug, infectious agent, gastric foreign body) and supportive therapy. Corticosteroids (see below) can be administered to suppress MPS activity while the etiologic agent is being eliminated, although this is not always beneficial. Doxycy-

cline (5 to 10 mg/kg PO q12-24h for 21 to 42 days) usually results in resolution of the signs in dogs and cats with mycoplasmosis and in dogs with ehrlichiosis.

#### **Immune Hemolytic Anemia**

IHA constitutes the most common form of hemolysis in dogs (see Chapter 104). Although two pathogenetic categories of hemolytic anemia are recognized (primary, or idiopathic, and secondary), most cases of IHA in dogs are primary (i.e., a cause cannot be found after exhaustive clinical and clinicopathologic evaluation). The immune-mediated destruction of RBCs can occur in association with drug administration (e.g.,  $\beta$ -lactam antibiotics, barbiturates) or vaccination. With the exception of the immune hemolysis secondary to hemoparasitism, IHA is rare in cats (although its prevalence is higher than 5 years ago). The clinical course in dogs is typically acute, but peracute presentations are also common.

In IHA, the RBCs become coated primarily with IgG, which leads to the early removal of the coated cells by the MPS, mainly in the spleen and liver. As a consequence spherocytes are generated; therefore the presence of spherocytes in the blood smear of a dog with anemia is highly suggestive of IHA. Spherocytes are difficult to identify in cats.

The typical patient with IHA is a middle-aged, female spayed Cocker Spaniel or small breed dog, although I have recently noticed a higher prevalence of IHA (and other immune-mediated cytopenias) in Golden Retrievers. Clinical signs in dogs with IHA include depression of acute (or peracute) onset, exercise intolerance, and pallor or jaundice, occasionally accompanied by vomiting or abdominal pain. Physical examination findings usually consist of pallor or jaundice, petechiae and ecchymoses (if immune thrombocytopenia is also present), splenomegaly, and a heart murmur. As previously noted, jaundice can be absent in dogs with IHA. A subset of dogs with acute (or peracute) IHA with icterus (and usually autoagglutination) shows clinical deterioration within hours or days of admission, resulting from multifocal thromboembolic disease or a lack of response to conventional therapy. I treat these dogs more aggressively than the typical dog with IHA (see next page).

Hematologic findings in dogs with IHA typically include strongly regenerative anemia, leukocytosis from neutrophilia with a left shift and monocytosis, increased numbers of nucleated RBCs, polychromasia, and spherocytosis. The serum (plasma) protein concentration is usually normal to increased, and hemoglobinemia or bilirubinemia may be present (i.e., pink or yellow plasma). As previously noted, autoagglutination is prominent in some dogs. Thrombocytopenia is also present in dogs with Evans syndrome or DIC.

The presence of polychromasia with autoagglutination and spherocytosis in a clinically ill dog with anemia of acute onset is virtually pathognomonic of IHA. In these cases a direct Coombs test is usually not necessary to confirm the diagnosis. In dogs that lack some of these physical examination and hematologic findings, a direct Coombs test

should be performed to detect Ig adsorbed to the RBC membrane.

The direct Coombs test is negative in approximately 10% to 30% of dogs with IHA, yet they tend to respond to immunosuppressive therapy (see below). In these cases enough Ig or complement molecules may be bound to the RBC membrane to induce the MPS to stimulate phagocytosis but not enough to result in a positive Coombs test. Hemolysis can occur in human beings with approximately 20 to 30 molecules of Ig bound to the RBC, whereas the direct Coombs test can only detect more than 200 to 300 molecules of Ig per cell. Another explanation for the findings in this subset of patients is that the previous administration of exogenous corticosteroids has resulted in decreased antibody binding to the surface of the RBCs.

Immunosuppressive doses of corticosteroids (equivalent to 2 to 4 mg/kg of prednisone q12-24h in the dog and up to 8 mg/kg q12-24h in the cat) constitute the treatment of choice for primary IHA. Although dexamethasone can be used initially, it should not be used as maintenance therapy for prolonged periods because of its higher potential to cause gastrointestinal tract ulceration or pancreatitis; in addition, if given on an alternate-day basis, it causes interference with the hypothalamic-pituitary-adrenal axis. In equivalent doses dexamethasone does not appear to be more beneficial than prednisone in dogs. In cats with IHA, I have used dexamethasone (4 mg/cat, PO, q1-2wk) with a high degree of success.

A high percentage of dogs treated with corticosteroids shows a marked improvement within 24 to 96 hours (Fig. 83-1). Corticosteroids act mainly by three different mechanisms: they suppress MPS activity, decrease complement and

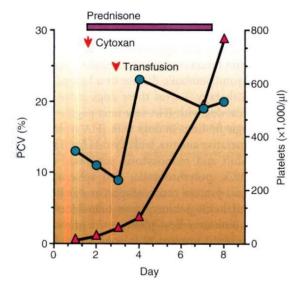


FIG 83-1
Response to treatment in a dog with immune hemolytic anemia (IHA) and immune-mediated thrombocytopenia (Evans syndrome). *PCV*, Packed cell volume; →, PCV; →, platelets; ↓, treatment administered.

antibody binding to the cells, and suppress Ig production. The first two effects are rapid in onset (hours), whereas the third effect is delayed (1 to 3 weeks).

I have observed a high number of dogs with acute or peracute IHA generally associated with icterus and autoagglutination that show a rapid deterioration and that usually die of thromboembolism of the liver, lungs, or kidneys despite aggressive corticosteroid therapy. Such animals are treated with cyclophosphamide (Cytoxan) at a dosage of 200 to 300 mg/m<sup>2</sup> given orally or intravenously in a single dose over a 5- to 10-minute period in conjunction with a single IV dose of dexamethasone sodium phosphate (1 to 2 mg/ kg). I also advocate the use of prophylactic heparin therapy because dogs with hemolysis are at high risk for DIC and thrombosis. In my practice heparin therapy of 50 to 75 IU/kg is routinely given subcutaneously every 8 hours. These dosages of heparin usually do not result in therapy-related prolongation of the activated clotting time (ACT) or the activated partial thromboplastin time (Aptt), tests used routinely to monitor heparinization. The use of low- or minidose aspirin (0.5 mg/kg q24-48h) has been associated with lower mortality rates in dogs with IHA. Because dogs with IHA are at high risk for thromboembolic events, I refrain from placing central venous lines; thrombosis of the anterior vena cava commonly leads to severe pleural effusion in these dogs. Aggressive fluid therapy should be administered in conjunction with these treatments in an attempt to flush the microaggregates of agglutinated RBCs from the microcirculation (Note: circulating blood does not clot). Importantly, however, is that depending on the degree of anemia, the resultant hemodilution may be detrimental to the patient. If deemed necessary, oxygen therapy should also be used, but it is rarely beneficial unless the HCT or Hb can be increased.

I have been using human intravenous IgG (HIVIGG-0.5 to 1.5 g/kg IV infusion, single dose) with a high degree of success in dogs with refractory IHA. This treatment is aimed at blocking the Fc receptors in the MPS with a foreign Ig, thus minimizing the phagocytosis of antibody-coated RBCs. This treatment appears to have other immunomodulatory effects as well. However, the product is moderately expensive (approximately \$300 to \$400 per dose for a 10-kg dog). This approach has had such an impact, however, that I frequently use it as the first line of therapy in dogs with severe IHA.

Drugs used for the maintenance treatment of dogs with IHA include prednisone (1 mg/kg PO q48h) and azathioprine (50 mg/m² PO q24-48h), used either singly or in combination. Azathioprine is associated with few adverse effects, although close hematologic and serum biochemical monitoring is necessary because of its potential to suppress bone marrow function and cause mild hepatopathy. A dose reduction is necessary if myelosuppression or hepatotoxicity occurs; occasionally azathioprine must be discontinued in dogs with hepatotoxicity. In cats, chlorambucil is an effective immunosuppressor with very low toxicity; I have used it successfully in cats with IHA, immune-mediated thrombo-

cytopenia, or other cytopenias at a dosage of 20 mg/m² PO q2wk. In general, dogs and cats with IHA require prolonged (often lifelong) immunosuppressive treatment. Whether an animal requires continuous treatment is determined by trial and error; decremental doses of the immunosuppressive drug(s) are administered for a given period (usually 2 to 3 weeks), at which time the patient is reevaluated clinically and hematologically. If the PCV has not decreased or has increased and the patient is clinically stable or has shown improvement, the dose is reduced by 25% to 50%. This procedure is repeated until the drug is discontinued or the patient relapses. In the latter case, the previously used dosage that had beneficial effects is used again. In my experience, more than two thirds of dogs with IHA require lifelong treatment.

Alternative treatments for dogs with refractory IHA include danazol (5 to 10 mg/kg PO q12h), cyclosporine (10 mg/kg PO q12-24h), and possibly splenectomy. However, splenectomy has rarely been of benefit in dogs with IHA treated at my clinic.

Chlorambucil (20 mg/m² PO q2wk) appears to be the best induction and maintenance agent in cats with IHA refractory to corticosteroids or in those who develop corticosteroid-induced diabetes mellitus. In my experience azathioprine causes pronounced myelosuppression in this species and should not be used.

One of the biggest dilemmas the clinician faces in the treatment of a dog with IHA is whether to administer a transfusion of blood or blood products. As a general rule, a transfusion should not be withheld if it represents a lifesaving procedure. However, because patients with IHA are already destroying their own antibody-coated RBCs, they may also be prone to destroying transfused RBCs (although this has not been scientifically proven). My recommendation is to administer a transfusion to any animal with IHA that is in dire need of RBCs (i.e., withholding a transfusion would result in the animal's death). I usually pretreat these patients with dexamethasone sodium phosphate (0.5 to 1 mg/kg IV), administer fluids through an additional IV catheter, and continue the heparin therapy. Although cross-matching is indicated, time is usually of the essence; therefore non-crossmatched universal donor blood is frequently administered; moreover, if autoagglutination occurs, the results of a crossmatch may be difficult to interpret.

Another issue pertaining to transfusion in dogs with IHA autoagglutination deals with blood typing; if blood typing cards are used, the results will be false-positive for DEA 1.1 (see Principles of Transfusion Therapy, p. 1221). Finally, no rule of thumb exists (e.g., PCV value, lack of response to oxygen therapy) regarding when to administer a transfusion. The clinician should use his or her best clinical judgment to determine when a transfusion of blood or blood products is necessary (e.g., does the patient exhibit tachypnea, dyspnea, or orthopnea?). If available, universal donor packed RBCs should be used instead of whole blood because they deliver a high oxygen-carrying capacity in a smaller volume and administration usually does not result in hypervolemia.

A polymer of bovine Hg has been available for use in dogs with acute anemia that are in dire need of oxygen-carrying capacity (Oxyglobin, Biopure Corp., Cambridge, Mass.). This compound has a long shelf life; it does not require refrigeration, blood typing, or cross-matching. Administration of Oxyglobin typically results in clinical improvement of the signs associated with anemia, but the duration of response is limited (2 or 3 days). Because of the nature of this compound, the PCV does not increase after infusion (the Hg concentration does increase). Some laboratory test results may be difficult to obtain after infusion of Oxyglobin because of interference with colorimetric analysis. Unfortunately this product is not readily available for veterinarians at this time.

#### **NONREGENERATIVE ANEMIAS**

With the exception of anemia of chronic disease (ACD), nonregenerative anemias do not appear to be clinically as common as regenerative forms in dogs, whereas the opposite is true in cats.

Five forms of nonregenerative anemia are typically recognized in cats and dogs (see Box 83-3). Because IDA can be mildly to moderately regenerative and the RBC indices are typically different from those in other forms of nonregenerative anemia (microcytic, hypochromic versus normocytic, normochromic; see Boxes 83-3 and 83-4 and Tables 83-2 to 83-4), I prefer to classify it in a separate category. Anemia of endocrine disease is typically mild and usually is an incidental finding in dogs with hypothyroidism or hypoadrenocorticism (see Chapters 51 and 53). In general, most nonregenerative anemias and IDA in cats and dogs are chronic, thus allowing for physiologic adaptation to the decrease in the RBC mass. As a consequence, these types of anemia may be detected incidentally during the routine evaluation of a cat or dog, which to the owner is asymptom-



BOX 83-4

Classification and Causes of Nonregenerative Anemia in Cats and Dogs

#### ACD

Bone marrow disorders

- Bone marrow (or erythroid) aplasia-hypoplasia
- Myelophthisis
- Myelodysplastic syndromes
- Myelofibrosis
- Osteosclerosis/osteopetrosis

#### ΔPΓ

Acute blood loss or hemolysis (first 48-96 hours) Anemia of endocrine disorders

- Hypoadrenocorticism
- Hypothyroidism

ACD, Anemia of chronic disease; ARD, anemia of renal disease.

atic. In many cases (e.g., ACD) the anemia is mild and clinical signs are absent. Although most nonregenerative anemias are chronic, two situations are commonly encountered in which this form of anemia is acute: acute blood loss (first 48 to 96 hours) and peracute hemolysis. In these two instances the bone marrow has not yet had time to mount a regenerative reticulocyte response.

When evaluating dogs and cats with symptomatic nonregenerative anemias of acute onset, the clinician should try to answer the following questions:

- Has this patient had an acute blood loss or does it have hemolytic anemia and has not yet been able to mount a regenerative response (i.e., less than 48 to 96 hours have elapsed since the event)?
- Does this patient have chronic anemia but is now symptomatic because of intercurrent disease (e.g., heart failure, sepsis)?

Most clinical and clinicopathologic abnormalities in cats and dogs with nonregenerative anemia have been discussed (see p. 1209). In general, the RBCs in dogs and cats with nonregenerative anemias are normocytic and normochromic; however, the RBCs are usually macrocytic and normochromic in cats with FeLV- or FIV-related hypoproliferative anemias. As previously discussed, the RBC indices are microcytic and hypochromic in dogs and cats with IDA

The clinical evaluation of a cat or dog with nonregenerative anemia differs radically from that of a patient with regenerative forms because the absence of regeneration reflects primary or secondary bone marrow abnormalities (e.g., bone marrow disorder, ACD). Therefore after extramarrow causes have been ruled out by performing a physical examination and a serum biochemical profile and urinalysis, a bone marrow aspiration or biopsy is indicated in these patients.

#### **ANEMIA OF CHRONIC DISEASE**

ACD is the most common form of nonregenerative anemia in cats and dogs; however, because it is mild, it almost never results in clinical signs of anemia and the patients are usually evaluated as a consequence of their primary disorder (e.g., cancer, infection). ACD develops secondary to a variety of chronic inflammatory, degenerative, or neoplastic conditions. Although the term anemia of chronic disease implies a chronic onset, it has recently been established that cats can develop ACD in as little as 2 weeks. However, some of those cats were receiving fluid therapy that may have resulted in hemodilution (Ottenjan et al., 2006). In most cats with ACD the PCV percentage values range from the high teens to the mid-20s, whereas in dogs they range from the mid-20s to the low 30s. Therefore ACD can usually be excluded in dogs with PCVs of less than 20% and in cats with PCVs of less than 17% to 18%. The RBC indices are normocytic and normochromic, and the CBC may also reflect the nature of the primary problem (e.g., leukocytosis, neutrophilia, monocy-



**TABLE 83-5** 

Distinguishing Features of ACD and IDA in Dogs

PARAMETER	ACD	IDA
Serum iron concentration	<b>↓</b>	$\downarrow\downarrow$
Total iron-binding capacity	Ν	NÎ
Percentage saturation	$\downarrow$	$\downarrow \downarrow$
Bone marrow iron stores	<b>↑</b>	$\downarrow$
Platelet count	Ν, ↓, ↑	$\uparrow$ , $\uparrow \uparrow$
Fecal occult blood	N	+(-)
Ferritin	N	1

ACD, Anemia of chronic disease; IDA, iron deficiency anemia;  $\downarrow$ , low;  $\downarrow\downarrow$ , markedly low;  $\uparrow$ , high;  $\uparrow\uparrow$ , markedly high; N, normal; +(-), positive or negative.

tosis, hyperproteinemia resulting from a polyclonal gammopathy); some cats with ACD have microcytic hypochromic RBC indices, a condition that mimics IDA.

Sustained inflammatory or neoplastic processes cause iron to be sequestered within the bone marrow MPS, and it is therefore not available to the erythroid precursors for normal erythropoiesis. This unavailability of iron is mainly mediated by lactoferrin and other acute-phase reactants released from neutrophils during inflammation. In cats and dogs with ACD, the serum iron concentration and total ironbinding capacity (TIBC, or transferrin concentration) are usually decreased and the Hb saturation is low, but iron stores in the bone marrow are increased (Table 83-5). Although serum ferritin concentrations are the main feature that distinguishes ACD from IDA (i.e., high in ACD and low in IDA) in human beings, the results of ferritin assays in dogs and cats with IDA and ACD are not as clear cut. Therefore, to conclusively differentiate ACD from IDA, evaluation of bone marrow iron stores by Prussian blue staining is important. After a diagnosis of ACD has been confirmed, every effort should be made to identify the cause of the problem if it is not already evident.

Dogs and cats with ACD usually do not require specific or supportive therapy because treatment of the primary disorder causes the anemia to resolve. Although some have advocated the use of anabolic steroids in dogs and cats with ACD, these agents appear to be of little or no benefit.

#### **BONE MARROW DISORDERS**

Neoplastic, hypoplastic, or dysplastic bone marrow disorders can result in anemia and other cytopenias. In these conditions a "crowding out" of the normal erythroid precursors by neoplastic or inflammatory cells (myelophthisis), a paucity or absence of erythroid precursors (hypoplasia or aplasia, respectively), or a maturation arrest of the erythroid precursors (dysplasia) occur. All these disorders, with the exception of pure RBC aplasia (PRCA) (see following section), typically affect more than one cell line and the patients are bicytopenic or pancytopenic (see Chapter 86).

In general, these disorders are chronic and the clinical signs are those of anemia (see p. 1209) with or without signs of the underlying disorder. Although some information regarding the pathogenesis of this type of anemia can be obtained by evaluating the clinical and hematologic data, a definitive diagnosis is usually made on the basis of the cytologic or histopathologic appearance of a bone marrow specimen and, possibly, the results of serologic tests or PCR for infectious agents (e.g., FeLV, FIV, Ehrlichia canis).

#### Bone Marrow (or Erythroid) Aplasia-Hypoplasia

Bone marrow aplasia-hypoplasia is characterized by aplasia or hypoplasia of all the bone marrow cell lines (bone marrow aplasia-hypoplasia or aplastic pancytopenia) or the erythroid precursor (RBC aplasia-hypoplasia or PRCA). This form of anemia (or combined cytopenias) can be caused by a variety of agents or disorders (see Chapter 86) (Box 83-5). The following discussion pertains to PRCA.



BOX 83-5

Bone Marrow Disorders in Cats and Dogs

#### Marrow (or Erythroid) Aplasia-Hypoplasia

FeLV (C)

Immune-mediated disorders (D, C)

Estrogen (D)

Phenylbutazone (D)

Other drugs (D, C)

Idiopathic (D, C)

#### Myelophthisis

Acute leukemias (D, C)

Chronic leukemias (D > C)

Multiple myeloma (D, C)

Lymphoma (D, C)

Systemic mast cell disease (C > D)

Malignant histiocytosis (D > C)

Metastatic carcinoma (rare D, C)

Histoplasmosis (rare D, C)

#### **Myelodysplastic Syndromes**

FeLV (C)

FIV (C)

Preleukemic syndrome (D, C)

Idiopathic (D, C)

#### **Myelofibrosis**

FelV (C)

Pyruvate kinase deficiency anemia (D) Idiopathic (D, C)

idiopullic (D, C)

#### Osteosclerosis/Osteopetrosis

FelV (C)

FeLV, Feline leukemia virus; FIV, feline immunodeficiency virus; D, dog; C, cat.

Clinically, dogs and cats with PRCA are evaluated because of the clinical signs already discussed. In contrast to ACD, in which the degree of anemia, and thus the severity of the clinical signs, is mild, cats and dogs with PRCA usually have a PCV of less than 15% and are therefore symptomatic. Hematologically, severe (normocytic normochromic) nonregenerative anemia is usually the only abnormality; macrocytosis in the absence of reticulocytes is a consistent finding in cats with FeLV- or FIV-related PRCA, and mild microcytosis can occasionally be present in dogs with PRCA. The large RBC volume in cats with retroviral infections is attributed to the erythroid dysplasia or dyserythropoiesis induced by the virus. Dogs with PRCA occasionally have circulating spherocytes, pointing toward an immune basis for the anemia. The direct Coombs test is also positive in more than half of these dogs, and their anemia responds to immunosuppressive therapy. Cats and dogs with bone marrow aplasia-hypoplasia are pancytopenic (see Chapter 86).

In addition to the above, FeLV and FIV testing should be done in cats with PRCA. A bone marrow aspiration or biopsy specimen should also be obtained to rule out other bone marrow disorders.

The FeLV envelope protein p15E suppresses erythropoiesis in vitro and is postulated to cause PRCA in FeLV-infected cats. The anemia in these cats is usually chronic and severe (a PCV of 5% to 6% is relatively common), and despite supportive therapy the condition of the patient deteriorates, leading the owners to request euthanasia. The supportive treatment of these cats includes whole blood or packed RBC transfusions as needed; the interval between transfusions usually shortens with each transfusion until the cat needs transfusions weekly. Anabolic steroids may be beneficial in some cats, although no clinical evidence supports this. Interferon administered orally may improve clinical signs (without resolution of the anemia) in some of these cats (see Chapter 102).

FeLV-negative cats with PRCA often have a positive direct Coombs test and frequently benefit from immunosuppressive doses of corticosteroids; I typically use 4 mg of dexamethasone (per cat) once every 1 to 2 weeks instead of the conventional prednisone or prednisolone daily to every other day. This steroid formulation is safe and effective, and I have not yet seen secondary diabetes mellitus in the cats treated. The use of human recombinant erythropoietin (Epo) (see below) does not appear to be indicated in these cats because their endogenous Epo activity is higher than that of normal cats. In addition, the long-term use of human recombinant Epo may lead to the development of anti-Epo antibodies and resultant refractory anemia.

PRCA of presumptive immune origin is relatively common in dogs and cats. The postulated mechanism is similar to that of IHA, except that in PRCA the antibodies (or cell-mediated immunity) are directed against the erythroid precursors. Humoral factors (antibodies) that block erythropoiesis in vitro have been well characterized in dogs with PRCA. As previously discussed, the direct Coombs test result is positive in some of these dogs (60%) and cats (50%),

and they respond well to immunosuppressive and supportive therapy. Bone marrow aspirates in dogs and cats with PRCA reveal either erythroid hypoplasia or hyperplasia of the early erythroid precursors and a maturation arrest at the rubricyte or metarubricyte stage. This poses an interesting situation because most clinical pathologists use the term "PRCA" only for the dogs and cats that have crythroid hypoplasia and "IHA with delayed erythroid regeneration" for those with erythroid hyperplasia and a maturation arrest. However, from a clinical standpoint both situations behave the exact way and respond to the same treatment. Therefore I prefer to use the term PRCA for dogs and cats with either of these bone marrow cytologic findings.

The same treatment as that used during the maintenance phase of IHA is recommended for these dogs (prednisone 2 to 4 mg/kg PO q24-48h and/or azathioprine 50 mg/m<sup>2</sup> PO q24-48h). In cats, I have successfully used dexamethasone alone (as previously discussed) or in combination with chlorambucil (Leukeran) at a dosage of 20 mg/m<sup>2</sup> given orally every 2 weeks. Responses occur in approximately 70% to 80% of the patients, but clinical and hematologic recovery may take 2 to 3 months; long-term (lifelong) treatment is usually required. Supportive treatment and transfusions of blood or packed RBCs are sometimes necessary. Because these patients are normovolemic, the latter is preferable. In addition, because transfusions may need to be administered on an ongoing basis, cross-matching is recommended before the administration of each transfusion. Of note, in dogs one of the mechanisms of adaptation to chronic hypoxia (e.g., anemia) is an increase in the intraerythrocytic 2,3diphosphoglycerate (2,3-DPG) concentration, resulting in a lower oxygen affinity (i.e., the delivery of oxygen to the tissues is facilitated). Therefore, because stored RBCs have lower concentrations of 2,3-DPG, the transfused cells have a higher affinity for oxygen. As a result the transfusion of stored blood to a patient with chronic anemia may result in transient decompensation because approximately 24 hours is usually required for the transfused, stored RBCs to regain 50% of the normal 2,3-DPG concentrations and get "recharged."

#### Myelophthisis, Myelodysplastic Syndromes, Myelofibrosis, Osteosclerosis-Osteopetrosis

These disorders are discussed in Chapter 86.

#### ANEMIA OF RENAL DISEASE

The kidney is the main site of production of Epo, the principal stimulus of erythropoiesis. In addition, in dogs and cats with chronic renal failure, the life span of RBCs is considerably shorter and subclinical to clinical gastrointestinal tract bleeding is present; high concentrations of parathyroid hormone also suppress crythropoiesis. Because of these factors, anemia is common in such patients. The anemia is usually normocytic and normochromic, with few or no reticulocytes. HCT levels in dogs and cats with anemia of renal disease (ARD) are usually in the 20% to low 30% range,

although HCT levels in the teens are common. Of note, the HCT in these patients is usually that low only after they have undergone intensive fluid therapy (i.e., on presentation the anemia is not that severe because the patients are markedly dehydrated).

Improvement in renal function may result in marginal increases in the RBC mass. Anabolic steroids are rarely beneficial in improving the anemia in these patients. Human recombinant Epo (Epogen, Amgen, Thousand Oaks, Calif.) has been used successfully to treat anemia in cats and dogs with chronic renal failure. A dose of 100 to 150 IU/kg given subcutaneously twice weekly is administered until the HCT returns to a target value (usually 20% to 25%); the interval between injections is then lengthened for maintenance therapy. The HCT usually returns to normal within 3 to 4 weeks of the start of treatment. Given the fact that this Epo is foreign to dogs and cats, an appropriate antibody response usually nullifies the beneficial effects of long-term therapy (6 to 8 weeks) in more than 50% of the patients.

#### ACUTE AND PERACUTE BLOOD LOSS OR HEMOLYSIS (FIRST 48 TO 96 HOURS)

After an acute episode of blood loss or hemolysis, bone marrow takes approximately 48 to 96 hours to release enough reticulocytes to result in regeneration. Therefore blood loss and hemolytic anemias are nonregenerative during the initial phases of recovery.

In most dogs and cats with acute blood loss, profound bleeding is either historically or clinically evident. If no obvious cause of bleeding is found or if the patient is bleeding from multiple sites, the hemostatic system should be evaluated in search of a coagulopathy (see Chapter 89). Sites of internal bleeding should be evident after a complete physical examination is performed.

Once the bleeding has been stopped, the anemia typically resolves within days to weeks. The initial management of a bleeding episode should include supportive therapy and IV crystalloids or plasma expanders. If necessary, blood or packed RBCs or Hg solutions should be administered.

The management of dogs with peracute hemolysis was discussed earlier in the chapter.

#### SEMIREGENERATIVE ANEMIAS

#### IRON DEFICIENCY ANEMIA

IDA is traditionally classified as nonregenerative even though mild to moderate regeneration usually occurs. Moreover, as previously discussed, the RBC indices in dogs and cats with IDA are microcytic and hypochromic, distinguishing it from other forms of nonregenerative anemia, which are normocytic and normochromic. When evaluating the CBC of a dog with microcytic hypochromic anemia, the clinician must remember that microcytosis occurs in some breeds (e.g., Akita, Shiba Inu, Sharpei) and in dogs with other disorders, such as portosystemic shunts (see Table 83-2).

This form of anemia is well characterized in dogs with chronic blood loss. In cats, IDA has been well documented only in wearling kittens, in whom iron supplementation results in rapid resolution of the clinical and hematologic abnormalities. IDA is extremely rare in adult cats, and I have seen it primarily in association with chronic blood loss in cats with gastrointestinal (GI) lymphoma. Given its rarity in cats, the following discussion of IDA pertains primarily to dogs.

Chronic blood loss leading to iron depletion is common in dogs with GI tract bleeding caused by neoplasia, gastric ulcers, or endoparasites (e.g., hookworms) and in those with heavy flea infestation. Other causes of chronic blood loss, such as urogenital bleeding and iatrogenic bloodletting, are extremely rare. In my experience the most common cause of symptomatic IDA in dogs that present for evaluation of signs associated with anemia is GI neoplasia.

Dogs with IDA are typically evaluated because of the signs of the anemia or because of GI tract signs such as diarrhea, melena, or hematochezia. Mild IDA is occasionally recognized during the routine evaluation of heavily parasitized dogs (mostly pups). Hematologically, most dogs with IDA have microcytic, hypochromic indices, mild reticulocytosis (1% to 5%), a high RBC distribution width (RDW) with an occasional bimodal population of RBCs, thrombocytosis, low serum iron and TIBC (transferrin) concentrations, an extremely low percentage of saturation (usually less than 10%), a low serum ferritin concentration, and low iron stores in the bone marrow (see Box 83-5). The RDW generated by a particle counter represents a histogram of RBC sizes; a high RDW is indicative of anisocytosis. The typical tetrad of hematologic abnormalities in dogs with IDA is microcytosis, hypochromasia, mild regeneration, and thrombocytosis.

Because the most common cause of IDA in adult dogs is chronic GI tract bleeding, the stools should always be evaluated for occult blood with commercially available kits (see Chapter 29); if the results are negative, they should be evaluated again two or three times during a period when the animal is not eating canned dog food (myoglobin in canned dog food can occasionally result in false-positive reactions). If occult blood is present in the stool, a GI tract neoplasm should be ruled out. Tumors commonly associated with IDA in dogs include GI stromal tumors (GISTs), such as leiomyomas, leiomyosarcomas, and true GISTs; lymphomas; and carcinomas. In dogs with IDA, positive fecal blood test results, and lack of clinical signs associated with the GI tract, the most likely diagnosis is a jejunal tumor (usually a GIST); I refer to these tumors as the "silent" GI neoplasms.

Another condition that can lead to IDA is chronic upper GI tract bleeding secondary to gastroduodenal ulceration, although most of these dogs have overt clinical signs associated with the GI tract (e.g., vomiting, hematemesis, weight loss). In pups or kittens with IDA, fecal flotation or a direct smear for hookworms and a thorough physical examination (to search for fleas) are mandatory because these are the two most common causes of IDA in young dogs and cats.

IDA usually resolves within 6 to 8 weeks after the primary cause has been eliminated. Oral or intramuscular iron supplementation is usually not necessary to hasten the resolution of the hematologic abnormalities; a sound commercial diet usually achieves the same effect. As a general rule, if the cause can be eliminated, I do not use iron supplementation. The dietary iron requirement for adult dogs and cats is approximately 1.3 mg/kg/day.

#### PRINCIPLES OF TRANSFUSION THERAPY

In the past 2 decades veterinary transfusion medicine has advanced radically. Several commercial blood banks are now available for pets, and most of them store blood components derived from processing units of whole blood or collected by apheresis. In a typical situation a unit of blood is spun immediately after collection, and packed RBCs (pRBCs) and fresh frozen plasma (FFP) stored at -20° C to -30° C are prepared; the pRBCs are preserved by adding a nutrient solution, and can be stored for up to 5 weeks. After 1 year of storage at -20° C to -30° C, FFP loses the labile clotting factors (V and VIII) and is referred to as stored plasma (SP) or frozen plasma (FP). Some blood banks prepare platelet-rich plasma (PRP) or platelet concentrates by apheresis. If FFP is allowed to warm up in a refrigerator, when it reaches approximately 4° C to 6° C a sludge forms in the bottom of the bag. That sludge can be separated by a short centrifugation, yielding cryoprecipitate (CRYO), a small volume rich in factor VIII, fibringen, and von Willebrand factor (vWF); the supernatant is referred to as cryo-poor plasma.

The transfusion of whole blood or blood components (e.g., pRBCs, PRP, FFP, CRYO, or SP) is indicated in several clinical situations. Whole blood or pRBC transfusion is most commonly required to restore the oxygen-carrying capacity in patients with anemia. Whole blood should be used if the anemic patient is hypovolemic or if it needs clotting factors, whereas pRBCs are recommended for normovolemic dogs and cats with anemia (i.e., PRCA, ARD, hemolysis). Transfusion therapy should be used with caution in animals with IHA (see p. 1217) because a massive transfusion reaction may occur; in those patients, Hg derivatives may be a better alternative if available.

Clotting factor deficiencies (see Chapter 87) resulting in hemorrhage can be corrected through the administration of whole fresh blood (if a considerable blood loss has occurred) or, more ideally, FFP or SP. Cryoprecipitate contains a high concentration of factor VIII and vWF, so it is typically used in dogs with hemophilia A or von Willebrand disease. Cryopoor plasma is a good source of clotting factors (except for factor III and vWF) and albumin. PRP or platelet transfusions, if available, can be used in dogs and cats with severe thrombocytopenia resulting in spontaneous bleeding (Table 83-6). However, the platelet count of the recipient is rarely raised enough to halt bleeding. PRP and platelet transfusions are of no benefit in patients with peripheral platelet destruction (e.g., immune-mediated thrombocytopenia) because



#### Practical Use of Blood Components

	WHOLE BLOOD	PRBCs	STORED PLASMA	FFP	CRYO	CRYOPOOR
Hypovolemic anemia	+++	++	_	_		_
Isovolemic anemia	+	+++	_	_		-
vWD	_	<u></u>	_	+++	++++	_
Hemophilia A	_	_	_	+++	++++	
Hemophilia B	_	_	+++	++		++++
Rodenticide toxicity	_	_	<del>-}-}-</del>	++	_	++++
Hypoalbuminemia		_	++	+	_	++++
Liver disease	-	_	++++	++	_	1   1   1
Pancreatitis	_	_	++++	+++	_	++++
AT deficiency	_	-	++++	+++	Aleman	++++
DIC	++	+	++	++++	_	++

PRBCs, Packed red blood cells; FFP, fresh frozen plasma; Cryo, cryoprecipitate; Cryopoor, cryo-poor plasma; vWD, von Willebrand disease; AT, antithrombin; DIC, disseminated intravascular coagulation; – to ++++, least indicated to best indicated.

the platelets are removed from the circulation immediately after the transfusion. Transfusion with whole fresh blood, PRP, or FFP is also indicated for the management of patients with DIC (see Chapter 87).

Less frequently, plasma is prescribed to correct hypoalbuminemia. However, only rarely can relevant increases in the recipient's serum albumin concentration be achieved. Colloids or human albumin solutions are more effective in restoring plasma oncotic pressure.

#### **BLOOD GROUPS**

Several blood groups have been recognized in dogs; these include dog erythrocyte antigen (DEA) 1.1 and 1.2 (formerly known as blood group A) and DEA 3 through 8. Dogs do not have naturally occuring antibodies against blood group antigens; therefore they can only acquire them after receiving a transfusion or after pregnancy. Transfusion reactions can occur if blood positive for DEA 1.1, 1.2, or 7 is transfused, so donors should be negative for those antigens. However, clinically relevant acute hemolytic transfusion reactions are extremely rare in dogs. Transfusion of blood from a donor who has not been typed and has never been pregnant or transfused to a recipient, independently of their blood types, is generally safe.

Blood groups in cats include A, B, and AB. Cats tested in the United States have almost exclusively been type A; the prevalence of type B cats varies greatly from region to region and among breeds. Breeds in which 15% to 30% of the cats are type B include Abyssinian, Birman, Himalayan, Persian, Scottish Fold, and Somali; breeds in which more than 30% of cats are type B include the British Shorthair and the Devon Rex. Because fatal transfusion reactions commonly occur in type B cats receiving type A blood, cats should always be cross-matched or typed before receiving a transfusion. In those cases a type B cat should be used as a donor. All the type B cats seen in our clinic in the past 5 years have

been domestic short-haired cats. Blood typing is also vital in cattery situations to prevent neonatal isoerythrolysis in type A or AB kittens born to type B queens.

#### **CROSS-MATCHING AND BLOOD TYPING**

Cross-matching is an alternative to blood typing in in-house donors or animals that have had prior transfusions, in cats, or in animals that will require multiple transfusions. Cross-matching detects many incompatibilities but does not guarantee complete compatibility. Rapid, cage-side blood typing cards for DEA 1.1 in dogs and for groups A and B in cats are commercially available (RapidVet-H, DMS Laboratories, Flemington, NJ). A kit for rapid cross-matching will soon be commercially available.

#### **BLOOD ADMINISTRATION**

Refrigerated blood may be warmed before or during administration, particularly in small dogs or cats; excessive heat should be avoided, however, because fibrinogen precipitation or autoagglutination may occur. I typically do not warm blood or pRBCs before administration. The administration set should have a filter in place (Baxter International, Deerfield, Ill.) to remove clots and other particulate matter, such as platelet aggregates. The blood is usually administered by way of the cephalic, saphenous, or jugular veins. However, intraosseous infusion may be performed in small animals, neonates, or animals with poor peripheral circulation. To administer fluids or blood intraosseously, the skin over the femur is surgically prepared and the skin and periosteum of the femoral trochanteric fossa are anesthetized with 1% lidocaine. A bone marrow needle (18 gauge) is placed into the marrow cavity parallel to the shaft of the femur. Suction with a 10-mL syringe should yield marrow elements (fat, spicules, and blood), confirming correct placement of the needle. The blood is administered through a standard blood administration set.

The recommended rate of administration is variable but should not exceed 22 mL/kg/day (up to 20 mL/kg/hr can be used in hypovolemic animals). Dogs and cats in heart failure may not tolerate a rate of more than 5 mL/kg/day. To prevent bacterial contamination, blood should not be exposed to room temperature during administration for longer than 4 to 6 hours (blood is considered to be contaminated if it is at room temperature for more than 6 hours). If necessary, two smaller volumes of blood can be administered in succession. Blood should never be administered with lactated Ringer's solution because of the calcium chelation with citrate and consequent clot formation that may occur. Normal saline solution (0.9% NaCl) should be used instead. A simple rule of thumb to predict the increase in the recipient's HCT is to remember that 2.2 mL/kg (or 1 mL/lb) of transfused whole blood will raise the HCT by 1% if the donor has an HCT of approximately 40%.

## COMPLICATIONS OF TRANSFUSION THERAPY

Transfusion-related complications can be divided into those that are immunologically mediated and those that are of nonimmunologic origin. Immune-mediated reactions include urticaria, hemolysis, and fever. Non-immune-mediated complications include fever resulting from the transfusion of improperly stored blood, circulatory overload, citrate intoxication, disease transmission, and the metabolic burden associated with the transfusion of aged blood. Signs of immediate immune-mediated hemolysis appear within minutes of the start of transfusion and include tremors, emesis, and fever; these are extremely rare in dogs but common in cats receiving incompatible blood products. Delayed hemolytic reactions are more common and are manifested primarily by an unexpected decline in the HCT after transfusion over days, in association with hemoglobinemia, hemoglobinuria, and hyperbilirubinemia. Circulatory overload may be manifested by vomiting, dyspnea, or coughing. Citrate intoxication occurs when the infusion rate is too great or the liver is not able to metabolize the citrate. Signs of citrate intoxication are related to hypocalcemia and include tremors and cardiac arrhythmias. If signs of a transfusion reaction are recognized, the transfusion must be slowed or halted.

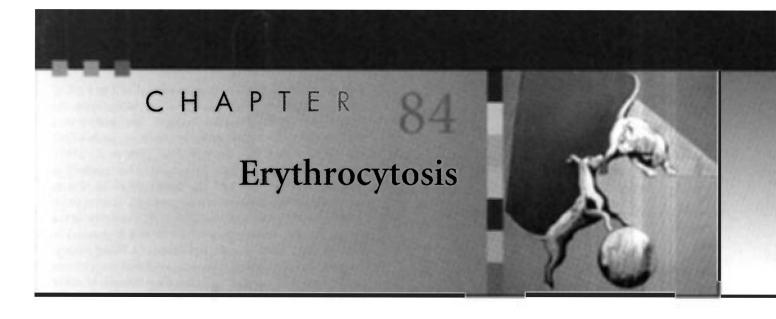
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#### CHAPTER OUTLINE

**DEFINITION AND CLASSIFICATION** 

#### **DEFINITION AND CLASSIFICATION**

Erythrocytosis is defined as an increase in the circulating red blood cell (RBC) mass and is manifested hematologically as an increase in the packed cell volume (PCV) or hematocrit (HCT) above reference values. Because determination of the RBC mass in a clinical setting is cumbersome and impractical, a diagnosis of erythrocytosis is typically made on the basis of the high HCT, not an increased RBC mass. Certain dog breeds, such as sight hounds, have HCT values above the reference range for the species; this also occurs in dogs that live at high altitudes. For example, normal retired racing Greyhounds can have a HCT as high as 70%. An increase in the RBC numbers may lead to severe hemorheologic alterations, resulting in clinical signs secondary to hyperviscosity. Although the term polycythemia is commonly used to refer to this hematologic abnormality, it is incorrect because the term actually means an increase in the numbers of all circulating cells (-poly means multiple).

On the basis of its pathogenesis, erythrocytosis can be classified as either relative or absolute (Box 84-1). The term relative erythrocytosis refers to hemoconcentration (i.e., dehydration), and it is characterized by an increased PCV, usually in association with an increased serum or plasma protein concentration; in dogs and cats with relative erythrocytosis the RBC mass is normal. Dogs with hemorrhagic gastroenteritis (HGE) frequently have relative erythrocytosis associated with normal serum or plasma protein concentration; the reason for the lack of increase in the protein concentration is unknown, but the erythrocytosis resolves with appropriate fluid therapy. In absolute, or true, erythrocytosis the RBC mass is increased; it can be classified as primary or secondary depending on the pathogenesis and the serum erythropoietin (Epo) concentration or activity.

Primary erythrocytosis (polycythemia rubra vera [PRV]) results from an autonomous, Epo-independent proliferation of RBC precursors in the bone marrow and is considered a myeloproliferative disease. As a consequence, most dogs and cats with PRV have low to nondetectable serum Epo concentrations. Secondary erythrocytosis results from increased orthotopic (i.e., produced by the kidneys) or heterotopic (i.e., produced in sites other than the kidneys) Epo production. Orthotopic (physiologically appropriate) Epo production occurs in response to tissue hypoxia, such as that occurring at a high altitude and in the settings of chronic cardiopulmonary disease, right-to-left cardiovascular shunts, and carboxyhemoglobinemia. Tumor-associated erythrocytosis (i.e., heterotopic or orthotopic Epo production) has been observed in human beings with a wide variety of neoplasms, in dogs with renal masses, and in dogs with spindle cell sarcomas (nasal fibrosarcoma, schwannoma, and cecal gastrointestinal stromal tumor). Hormonal stimuli may also trigger erythrocytosis in animals with normal tissue oxygenation, such as in dogs with hyperadrenocorticism and cats with hyperthyroidism. At the author's clinic, secondary erythrocytosis is more common in dogs and PRV is more common in cats. However, erythrocytosis is rare in both species. Interestingly, although infiltrative renal diseases (e.g., lymphoma, feline infectious peritonitis) are common in cats, they rarely, if ever, result in secondary erythrocytosis.

#### **Clinical and Clinicopathologic Findings**

The clinical signs may occur acutely and consist primarily of functional abnormalities of the central nervous system (e.g., behavioral, motor, or sensory changes; seizures). In cats signs of a transverse myelopathy are common. A common manifestation of erythrocytosis in dogs is paroxysmal sneezing, attributed to increased blood viscosity in the nasal mucosa. Cardiopulmonary signs may occasionally be present. Although the erythrocytosis usually develops gradually, most affected animals do not exhibit clinical signs until the RBCs have reached a critical mass (or the PCV has reached a certain percentage). PCVs of 70% to 80% are relatively common in cats and dogs with absolute



Classification and Causes of Erythrocytosis in Cats and Dogs

#### Relative Erythrocytosis (Pseudoerythrocytosis)

Hemoconcentration

Absolute Erythrocytosis
Primary

**PRV** 

#### Secondary

Appropriate (i.e., secondary to decreased tissue oxygenation)

Pulmonary disease

Right-to-left cardiovascular shunts

High altitude

Hemoglobinopathies?

Inappropriate (normal tissue oxygenation)

Hyperadrenocorticism

Hyperthyroidism

Renal masses

Neoplasms in other areas

PRV, Polycythemia rubra vera;  $\it{?}$ , Not well documented in cats or dogs.

erythrocytosis. Physical examination and historical findings in dogs and cats with erythrocytosis may also include bright red mucous membranes (plethora), erythema, polyuria, polydipsia, splenomegaly, renal masses, or a neoplasm elsewhere.

Hematologic abnormalities are usually limited to the erythrocytosis, although thrombocytosis may be present in cats and dogs with PRV. Microcytosis caused by relative iron deficiency (i.e., the erythron is extremely active and is relatively iron deficient) is common in dogs with erythrocytosis.

#### **Diagnosis and Treatment**

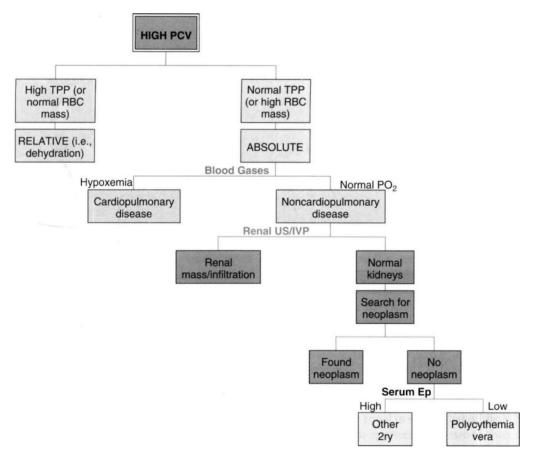
Relative erythrocytosis (i.e., dehydration) should be ruled out first. This is done primarily on the basis of the serum (or plasma) protein concentration, which is typically high in dogs and cats with this form of erythrocytosis. However, in certain circumstances, such as HGE, dogs may have a high HCT but a relatively normal serum protein concentration. Radioisotopic RBC mass determinations are commonly performed in human beings with erythrocytosis, but this test is usually not done in small animals.

The initial approach used in small animals with absolute erythrocytosis is to decrease the blood viscosity by reducing the number of circulating RBCs. This can be accomplished by performing therapeutic phlebotomies, in which a certain volume of blood (approximately 20 mL/kg) is collected from a central vein through a blood collection set. In cats a 19-gauge butterfly catheter coupled to a 60-mL syringe

containing 500 to 600 U of heparin diluted in 3 to 5 mL of saline solution is typically used to collect blood from the jugular vein under chemical restraint (the author uses sevoflurane inhalant anesthesia). Interestingly, leeches have recently been used in a cat with PRV (Nett et al., 2001). Gradual phlebotomy (5 mL/kg, repeated as needed) is recommended for dogs and cats with right-to-left shunts and erythrocytosis because an increased RBC mass appears to be the body's way of enhancing oxygen delivery to the tissues, thereby compensating for the chronic hypoxemia in these animals. Because sudden decreases in blood volume can result in marked hypotension, a peripheral vein catheter can be used to administer an equivalent volume of saline solution at the same time that blood is being collected. However, collapsing episodes during or immediately after phlebotomy are extremely rare. As a result of its high viscosity in patients with erythrocytosis, it may be extremely difficult to obtain blood through a relatively small (e.g., 19-gauge) catheter.

Once the patient's condition has been stabilized, the cause of the erythrocytosis should be sought (Fig. 84-1). The following approach is recommended. The patient's cardiopulmonary status should first be evaluated by auscultation, precordial palpation, thoracic radiography, or echocardiography (see Chapters 1 and 2). An arterial blood sample should be obtained for blood gas analysis to rule out hypoxemia and pulse oxymetry used to evaluate oxygenation. In some animals with erythrocytosis the blood viscosity is so high that the blood gas analyzer (which is usually flow dependent) cannot generate results; in this event a therapeutic phlebotomy should be performed before a sample is resubmitted for testing (i.e., the blood oxygen content [PO<sub>2</sub>] does not change after therapeutic phlebotomy). If the PO2 is normal, excretory abdominal ultrasonography or computerized tomography should be performed to determine whether masses or infiltrative lesions are present in the kidneys. If no such lesions are found, the patient most likely does not have renal secondary crythrocytosis, so a search for an extrarenal neoplasm should be conducted. A serum sample for determination of Epo activity or concentration should be sent for analysis to a reliable laboratory (e.g., Dr. Urs Giger, Department of Genetics, School of Veterinary Medicine, University of Pennsylvania). In the author's experience, bone marrow evaluations of cats and dogs with erythrocytosis are unrewarding; in most cases the only abnormality is a decreased myeloid/erythroid ratio as a result of erythroid hyperplasia.

If PRV is established in the animal, hydroxyurea (30 mg/kg PO q24h) is administered for 7 to 10 days, after which the dose can be gradually decreased or the dosing interval gradually lengthened to fulfill the patient's needs. Phlebotomy should be repeated as dictated by the patient's clinical signs. If the final diagnosis is secondary erythrocytosis, the primary disorder should be treated (e.g., surgery for a renal mass). The author and others have successfully used the hydroxyurea protocol in dogs with right-to-left shunts and secondary erythrocytosis (Moore & Stepien, 2001).



**FIG 84-1** Diagnostic approach to the dog or cat with erythrocytosis. *PCV*, Packed cell volume; *TPP*, total plasma protein; *RBC*, red blood cell; *US/IVP*, ultrasonography/intravenous pyelography; *Ep*, erythropoietin; *2ry*, secondary.

Most dogs and cats with PRV have extremely long survival times (longer than 2 years) if treated with hydroxyurea, with or without phlebotomies. Because this drug is potentially myelosuppressive, complete blood counts should be performed every 4 to 8 weeks and the dose adjusted according to the neutrophil count (see Chapter 80). The prognosis in dogs and cats with secondary erythrocytosis depends on the nature of the primary disease.

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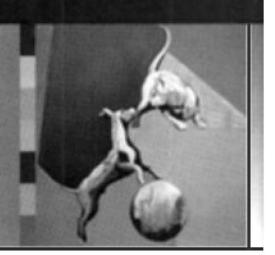
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### CHAPTER

## Leukopenia and Leukocytosis



#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS
NORMAL LEUKOCYTE MORPHOLOGY AND
PHYSIOLOGY
LEUKOCYTE CHANGES IN DISEASE

Neutropenia

Neutrophilia

Eosinopenia

Eosinophilia

Basophilia

Monocytosis

Lymphopenia

Lymphocytosis

#### **GENERAL CONSIDERATIONS**

The leukogram, evaluated as part of the complete blood count (CBC), includes a quantification of the total number of white blood cells (WBCs) and the differential WBC count. Although a specific disorder is rarely diagnosed on the basis of a leukogram, the information obtained may be useful in limiting the number of differential diagnoses or in predicting the severity of the disease and its prognosis. Sequential leukograms may also be helpful in monitoring a patient's response to therapy.

According to standard laboratory techniques, all nucleated cells are counted during a WBC count, including nucleated red blood cells (nRBCs). Differential leukograms determined by particle counters used at human referral laboratories are not valid for cats and dogs. New veterinary benchtop analyzers (LaserCyte, IDEXX, Westbrook, Maine; and CBC-Diff, Heska Corporation, Fribourg, Switzerland) provide reliable WBC total and differential counts. The LaserCyte provides a five-part differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), whereas the CBC-Diff provides a three-part differential count. As a general rule, when a benchtop hematology analyzer yields values outside the reference range or

the values are flagged, the clinician or a technician should carefully examine a blood smear.

Leukocytosis occurs if the WBC count exceeds the upper limit of normal for the species; leukopenia occurs if the WBC count is below the reference range. In some breeds of dogs (Belgian Tervuren, Greyhound) the WBC and neutrophil counts are frequently below the reference range for the species, thus resulting in an erroneous diagnosis of leukopenia and neutropenia in an otherwise healthy dog.

A differential WBC count may be reported in either relative (percentages) or absolute numbers (number of cells per microliter). However, the *absolute* leukocyte numbers, not the percentages, should always be evaluated because the latter may be misleading, particularly if the WBC count is very high or very low. For example, a total WBC of 3000/ L (or  $3 \times 10^9$ /L) and a differential WBC count of 90% lymphocytes and 10% neutrophils can lead to one of the following two conclusions:

- 1. According to the percentages alone, the dog has lymphocytosis and neutropenia; in this situation the clinician may erroneously focus on the "lymphocytosis" rather than the neutropenia.
- 2. According to the absolute numbers, the dog has severe neutropenia (300 cells/ L) with a normal lymphocyte count (i.e., 2700 cells/ L).

The latter obviously reflects the actual clinical situation. The clinician should then concentrate on determining the cause of the neutropenia and ignore the normal lymphocyte count.

#### NORMAL LEUKOCYTE MORPHOLOGY AND PHYSIOLOGY

From a morphologic standpoint, leukocytes can be classified as either polymorphonuclear or mononuclear. Polymorphonuclear cells include the neutrophils, eosinophils, and basophils; the mononuclear cells include the monocytes and lymphocytes. Their basic morphologic and physiologic characteristics are reviewed elsewhere (Feldman et al., 2000).

The following morphologic changes have important clinical implications and should thus be recognized:

- 1. Neutrophils may become toxic in response to injury; toxic neutrophils display characteristic cytoplasmic changes, including basophilia or granulation, vacuolation, and Döhle bodies (small, bluish cytoplasmic inclusions that consist of aggregates of endoplasmic reticulum). This change occurs in the bone marrow and indicates that the neutrophils are losing the battle against the offending agent.
- Giant neutrophils, bands, and metamyelocytes are large, polyploidal cells that may result from skipped cell division; they represent yet another manifestation of toxic changes and are more common in cats than dogs.

Other neutrophil morphologic abnormalities recognized during a careful examination of blood smears include the Pelger-Huët anomaly (cats and dogs) and Chédiak-Higashi syndrome (cats). The Pelger-Huët anomaly occurs when the nucleus of polymorphonuclear leukocytes fails to divide, but the nuclear chromatin and cytoplasm maturation is complete (i.e., the nucleus has a bandlike appearance with mature, clumped chromatin). Cats and dogs with this anomaly typically have profound left shifts in the absence of clinical signs. On careful examination of the smear, however, the cells in the left shift are mature cells with nuclear hyposegmentation and not immature neutrophils. This anomaly may be acquired or inherited (autosomal dominant) and is usually considered of minimal clinical relevance. We have seen it primarily in Australian Cattle dogs and in dogs undergoing chemotherapy.

Chédiak-Higashi syndrome, a lethal autosomal recessive condition of Persian cats with smoke-colored haircoats and yellow eyes, is characterized by enlarged neutrophilic and eosinophilic granules in association with partial albinism, photophobia, increased susceptibility to infections, bleeding tendencies, and abnormal melanocytes.

Nuclear hypersegmentation (i.e., four or more distinct nuclear lobes) may result from a prolonged neutrophil transit time ("old" neutrophils). It occurs in dogs with hyperadrenocorticism, cats and dogs receiving corticosteroid therapy, and cats and dogs with chronic inflammatory disorders.

A basic review of neutrophil physiology follows. Three theoretical physiologic neutrophil compartments exist in the bone marrow (Fig. 85-1). The proliferative compartment is composed of dividing cells (myeloblasts, progranulocytes, and myelocytes); myeloblasts take approximately 48 to 60 hours to mature into metamyelocytes. The maturation compartment consists of metamyelocytes and band neutrophils; the transit time through this compartment is 46 to 70 hours. The storage compartment is composed of mature neutrophils; the transit time in this compartment is approximately

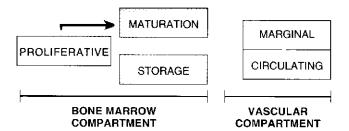


FIG 85-1 Theoretical neutrophil compartments in bone marrow and

50 hours, and it contains an estimated 5-day supply of neutrophils. Mature neutrophils leave the bone marrow by a random process that involves changes in cell deformability and adhesiveness.

Two neutrophil pools are present in the vascular compartment (see Fig. 85-1). The marginal neutrophil pool (MNP) consists of neutrophils that are adhered to the vascular endothelium (and are thus not counted during a CBC). The circulating neutrophil pool (CNP) consists of the neutrophils circulating in the blood (i.e., the cells counted during a differential WBC count). The total blood neutrophil pool is composed of the MNP plus the CNP. In dogs the CNP is approximately equal in size to that of the MNP. However, in cats the MNP is approximately two to three times the size of the CNP. The neutrophil has an average blood transit time of approximately 6 to 8 hours in dogs and 10 to 12 hours in cats, with all blood neutrophils replaced every 2 to 2.5 days. Once the neutrophils leave the blood vessel (by diapedesis), they normally do not return to the circulation and are lost in the lungs, gut, other tissues, urine, or saliva.

#### LEUKOCYTE CHANGES IN DISEASE

Because the lower limit for the reference range for basophil and monocyte counts is 0, basopenia and monocytopenia are not discussed.

#### **NEUTROPENIA**

Neutropenia is defined as an absolute decrease in the number of circulating neutrophils. It can result from decreased (or impaired) cell production within the bone marrow or from the increased margination or destruction of circulating neutrophils (Box 85-1). Neutropenia is relatively common in cats and dogs. The clinician should keep in mind, however, that normal cats may have neutrophil counts of 1800 to 2300/μL; this reference range is also true for Greyhounds.

In a recent study of 232 dogs and 29 cats evaluated in a teaching hospital (Brown & Rogers, 2001), infectious diseases (feline leukemia virus, feline immunodeficiency virus, parvovirus) were the most common comorbid conditions, accounting for almost 52% of the cases of neutropenia. Sepsis or endotoxemia accounted for 11% of the cases, as did drug-associated neutropenia (e.g., chemotherapy, phenobar-



#### Causes of Neutropenia in Cats and Dogs

#### Decreased or Ineffective Production of Cells in the Proliferating Pool

Myelophthisis (neoplastic infiltration of the bone marrow)

Myeloproliferative disorders (D, C)

Lymphoproliferative disorders (D, C)

Systemic mast cell disease (D, C) Malignant histiocytosis (D, C?)

Myelofibrosis (D, C)

Metastatic carcinoma (D?, C?)

#### Drug-induced neutropenia

Anticancer and immunosuppressive agents (C, D)

Chloramphenicol (C)

Griseofulvin (C)

Sulfa-trimethoprim (D, C)

Estrogen (D)

Phenylbutazone (D)

Phenobarbital (D)

Other

#### Toxins

Industrial chemical compounds (inorganic solvents, benzene)

Fusarium sporotrichiella toxin (C)

#### Infectious diseases

Parvovirus infection (D, C)

Retrovirus infection (feline leukemia virus, feline immunode-

ficiency virus) (C)

Myelodysplastic or preleukemic syndromes (C)

Cyclic neutropenia (C)

Histoplasmosis (D, C)

Ehrlichiosis (D, C)

Anaplasmosis (D, C)

Toxoplasmosis (D, C)

Early canine distemper virus infection (D)

Early canine hepatitis virus infection (D)

#### Other

Idiopathic bone marrow hypoplasia-aplasia (D, C)

Cyclic neutropenia of gray Collies (D)

Acquired cyclic neutropenia (D, C)
Steroid-responsive neutropenia (D, C)

#### Sequestration of Neutrophils in the Marginating Pool

Endotoxic shock (D, C)

Anaphylactic shock (D, C)

Anesthesia (D?, C?)

## Sudden, Excessive Tissue Demand, Destruction, or Consumption

Infectious diseases

Peracute, overwhelming bacterial infection (e.g., peritonitis, aspiration pneumonia, salmonellosis, metritis, pyothorax)

Viral infection (e.g., canine distemper or hepatitis, preclinical stage) (D)

Drug-induced disorders (D, C) (see above)

Immune-mediated disorders (D, C)

Paraneoplastic (D)

"Hypersplenism" (D?)

Common; relatively common; uncommon; D, dog; C; cat; ?, poorly documented.

bital, antibacterials); primary bone marrow disease was found in 4% of the patients. The cause of the neutropenia was unclear in 21% of the patients.

Clinical signs in neutropenic cats and dogs are usually vague and nonspecific; they include anorexia, lethargy, pyrexia, and mild gastrointestinal tract signs. Oral ulceration, a common feature of neutropenia in human beings, does not seem to occur in small animals. Neutropenia is frequently an incidental finding in an otherwise healthy dog or cat (i.e., the patient is asymptomatic). If the neutropenia is caused by peripheral neutrophil consumption (i.e., a septic process), most animals exhibit clinical signs. Dogs and cats with parvoviral enteritis have neutropenia in association with severe vomiting or diarrhea or both. Cats and dogs with neutropenia can occasionally present in septic shock (pale, hypoperfused, hypothermic) and should be treated aggressively.

The evaluation of neutropenic cats and dogs should include a detailed drug history (e.g., estrogen or phenylbutazone in dogs, griseofulvin in cats; see Box 85-1); vaccination

history (e.g., was the cat vaccinated against panleukopenia or the dog against parvoviral enteritis?); a complete physical examination and imaging in search of a septic focus; serologic, virologic, or molecular tests for infectious diseases (e.g., feline leukemia virus, feline immunodeficiency virus, canine ehrlichiosis, parvoviral enteritis); and, if necessary, bone marrow cytologic or histopathologic studies. Evaluation of changes in a blood smear is important in establishing the pathogenesis of the neutropenia. Benchtop hematology analyzers provide total neutrophil counts and do not distinguish mature neutrophils from bands, reemphasizing the value of evaluating the blood smear. If a dog or cat has anemia and/or thrombocytopenia in association with the neutropenia, particularly if the anemia is nonregenerative, a primary bone marrow disorder should be strongly suspected. If a dog or cat has regenerative anemia and spherocytosis in association with neutropenia, an immune-mediated disease should be considered a likely diagnosis.

The presence of toxic changes in the neutrophils or a left shift (see below) tend to suggest infection (i.e., toxic changes and left shifts are typically absent in dogs and cats with steroid-responsive neutropenia or primary bone marrow disorders). In a recent study of 248 dogs with toxic neutrophil changes conducted in Israel (Aroch et al., 2005) dogs with pyometra, parvoviral infection, peritonitis, pancreatitis, and septicemia were significantly, and not surprisingly, more likely to have toxic changes than those in the control group. Interestingly, toxic neutrophil changes were also significantly associated with acute renal failure, immune-mediated hemolytic anemia, and disseminated intravascular coagulation.

Evaluation of sequential leukograms in neutropenic dogs and cats is helpful in excluding transient or cyclic neutropenia (or cyclic hematopoiesis).

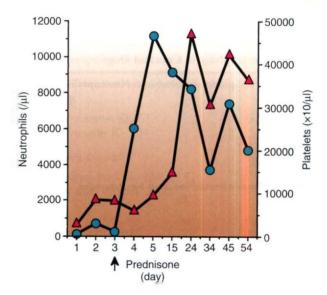
If the pathogenesis of neutropenia cannot be ascertained in an animal, sophisticated diagnostic techniques such as testing for antineutrophil antibodies, leukocyte nuclear scanning, or leukocyte kinetic studies can be performed. As previously noted, normal cats and Greyhounds can have low neutrophil counts. Therefore if a cat or a Greyhound with a neutrophil count of 1800 to 2300/µL is brought in for evaluation (or, more likely, if the "neutropenia" is detected during a routine hematologic evaluation), a conservative approach (e.g., repeat the CBC in 2 to 3 weeks) is indicated as long as no other clinical or hematologic abnormalities are found (e.g., left shift, toxic changes).

Because corticosteroid-responsive neutropenia has been well characterized in cats and dogs, if most infectious and neoplastic causes of neutropenia have been ruled out in an asymptomatic neutropenic animal, an in-hospital therapeutic trial of immunosuppressive doses of corticosteroids (prednisone, 2 to 4 mg/kg/day PO for dogs; 4 to 8 mg/kg/day PO for cats) can be instituted. Responses are usually observed within 24 to 96 hours of the start of treatment in such patients. Treatment is continued as it is for dogs with immune hemolytic anemia and other immune-mediated disorders (see Chapter 93) (Fig. 85-2).

Asymptomatic, afebrile neutropenic dogs and cats should be treated with broad-spectrum bactericidal antibiotics because they are at high risk for sepsis. The authors' drug of choice in dogs is sulfamethoxazole and trimethoprim, at a dosage of 15 mg/kg PO q12h; another drug that can be used in both dogs and cats is enrofloxacin (Baytril) at a dosage of 5 mg/kg PO q12-24h. Antibiotics with an anaerobic spectrum should not be used because they deplete intestinal anaerobes, a protective bacterial population.

Neutropenic febrile (or symptomatic) cats and dogs constitute a medical emergency and should be treated with aggressive intravenous antibiotic therapy. The authors' treatment of choice consists of a combination of ampicillin (20 mg/kg IV q8h) and enrofloxacin (5-10 mg/kg IV q24h).

Neutrophil production can be stimulated by the administration of human recombinant granulocyte colony-stimulating factor (G-CSF) (5  $\mu g/kg$  SQ q24h). Although results are quite spectacular, the responses are usually short lived because of the counteractive effects of anti-CSF antibodies produced by the affected dog or cat. Lithium carbonate



Response to therapy in a 6-year-old, female, spayed Airedale Terrier with steroid-responsive neutropenia and thrombocytopenia. Note the rapid response to immunosuppressive doses of prednisone. —, Polymorphonuclear neutrophils (in microliters); —, platelets (×10³/µl).

(10 mg/kg PO q12h) can increase the neutrophil counts in dogs; the therapeutic trough serum concentration of lithium is 0.8 to 1.5 mmol/L. This drug should be used with caution in dogs with decreased glomerular filtration rate because it is primarily excreted by the kidneys. Lithium carbonate does not appear to be effective in cats and may be toxic.

#### **NEUTROPHILIA**

Neutrophilia is defined as an absolute increase in the number of neutrophils; it is the most common cause of leukocytosis in dogs and cats. Several terms used to characterize neutrophilia are defined below.

The term mature neutrophilia refers to an increase in the number of segmented (mature) neutrophils without an increase in the number of immature forms (e.g., bands). Neutrophilia with a left shift refers to an increase in the number of both mature and immature neutrophils (more than 300/µL bands). A regenerative left shift is neutrophilia with increased numbers of immature neutrophils in which the number of immature forms does not exceed the number of mature neutrophils; most dogs and cats with a regenerative left shift have leukocytosis. A degenerative left shift occurs when the number of immature forms exceeds that of mature neutrophils; the number of the latter may be normal, low, or high. Degenerative left shifts are usually suggestive of an aggressive disease; toxic neutrophil changes (see previous section) are common in dogs and cats with degenerative left shifts. Disorders commonly associated with degenerative left shifts include pyothorax, septic peritonitis, bacterial pneumonia, pyometra, prostatitis, and acute pyelonephritis. The term extreme neutrophilia refers to situations in which the



#### Causes of Neutrophilia in Cats and Dogs

#### Physiologic or Epinephrine-Induced Neutrophilia

Fear (C)
Excitement (?)
Exercise (?)
Seizures (D, C)
Parturition (?)

#### Stress- or Corticosteroid-Induced Neutrophilia

Pain (?)
Anesthesia (?)
Trauma (D, C)
Neoplasia (D, C)
Hyperadrenocorticism (D)
Metabolic disorders (?)
Chronic disorders (D, C)

#### Inflammation or Increased Tissue Demand

Infection (bacterial, viral, fungal, parasitic) (D, C) Tissue trauma and/or necrosis (D, C) Immune-mediated disorders (D)

Neoplasia (D, C)
Metabolic (uremia, diabetic ketoacidosis) (D, C)
Burns (D, C)
Neutrophil function abnormalities (D)
Other (acute hemorrhage, hemolysis) (D, C)

**Common**; relatively common; uncommon; D, dog; C, cat; ₹, poorly documented.

neutrophil count is above 50,000/µI.; it can be associated with a left shift or mature neutrophilia. Diseases typically associated with extreme leukocytosis include septic foci (e.g., pyometra), immune-mediated diseases, hepatozoonosis, mycobacteriosis, and chronic myelogenous leukemia. A leukemoid reaction refers to a marked neutrophilia with a severe left shift, which includes metamyelocytes and myelocytes. It indicates severe inflammatory disease and may be difficult to distinguish from chronic granulocytic (myelogenous) leukemia (see Chapter 81).

Although a high percentage of cats and dogs with neutrophilia have underlying infectious disorders, neutrophilia is not synonymous with infection. Rather, neutrophilia in cats and dogs is commonly the result of inflammatory or neoplastic processes. Several disorders resulting in neutrophilia are listed in Box 85-2.

Of note, neutrophilia commonly results from endogenous epinephrine release (physiologic neutrophilia). This neutrophilia, which is associated with the release of neutrophils from the MNP, is transient (lasting 20 to 30 minutes after endogenous release of catecholamines) and is commonly associated with erythrocytosis and lymphocytosis (the latter primarily in cats).

The endogenous release or exogenous administration of corticosteroids results in stress- or corticosteroid-induced

neutrophilia, which is associated with decreased neutrophil egress from the vasculature and increased bone marrow release of neutrophils from the storage pool. Other hematologic changes typical of a stress leukogram include lymphopenia, eosinopenia, and monocytosis (the latter does not occur in cats). These abnormalities are commonly seen in sick dogs and cats.

Clinical signs in cats and dogs with neutrophilia are usually secondary to the underlying disorder. Pyrexia may or may not be present. If the patient has persistent neutrophilia, if the neutrophils display toxic changes (see p. 1229), or if a degenerative left shift is present, every effort should be made to identify a septic focus or an infectious agent promptly. The workup in such animals should include a thorough physical examination (e.g., abscess); thoracic and abdominal radiography (e.g., pneumonia, pleural or abdominal effusion); abdominal ultrasonography (e.g., peritonitis, pancreatic or hepatic abscess); and the collection of blood, urine, fluid, or tissue samples for cytology and bacterial and fungal cultures. As previously discussed, autologous or allogeneic neutrophils labeled with radionuclides (i.e., technetium 99m or indium 111) can be injected intravenously and the septic focus, or foci, identified by gamma camera imaging; an inflammatory focus can also be detected by radiolabeled ciprofloxacin.

The treatment of dogs and cats with neutrophilia is aimed at the primary cause. Empiric antibiotic therapy with a broad-spectrum bactericidal antibiotic (e.g., sulfa-trimethoprim, enrofloxacin, cephalosporin, amoxicillin) is an acceptable approach if a cause for the neutrophilia cannot be identified after exhaustive clinical and clinicopathologic evaluation or as the first line of treatment in a fairly asymptomatic dog or cat.

#### **EOSINOPENIA**

Eosinopenia is defined as an absolute decrease in the number of circulating eosinophils. It is commonly seen as part of the stress leukogram or with exogenous corticosteroid administration and is usually of little clinical relevance.

#### EOSINOPHILIA

Eosinophilia is defined as an absolute increase in the circulating eosinophil numbers. It is relatively common in small animals and can have a variety of causes (Box 85-3). Because eosinophilia is quite common in dogs and cats with parasitic disorders, no animal should undergo a thorough evaluation for eosinophilia before parasitic causes have been ruled out. In cats, flea infestation usually results in marked increases in the eosinophil count. In dogs, eosinophilia is frequently seen in roundworm and hookworm infestations or with dirofilariasis or dipetalonemiasis. Three additional relatively common causes of eosinophilia in cats include eosinophilic granuloma complex, bronchial asthma, and eosinophilic gastroenteritis. A clinical entity resembling feline hypereosinophilic syndrome has been reported in Rottweilers (Sykes et al.); in addition, lesions compatible with oral eosinophilic granulomas have been reported in Siberian Huskies.



#### Causes of Eosinophilia in Cats and Dogs

#### **Parasitic Disorders**

Ancylostomiasis (D) Dirofilariasis (D, C)

Dipetalonemiasis (D)

Ctenocephalidiasis (D, C)

Filaroidiasis (C)

Aelurostrongylosis (C)

Ascariasis (D, C)

Paragonimiasis (D, C)

#### **Hypersensitivity Disorders**

Atopy (D, C) Flea allergy dermatitis (D, C) Food allergy (D, C)

#### Eosinophilic Infiltrative Disorders

Eosinophilic granuloma complex (C) Feline bronchial asthma (C) Pulmonary infiltrates with eosinophils (D) Eosinophilic gastroenteritis/colitis (D, C)

Hypereosinophilic syndrome (D, C)

#### Infectious Diseases

Upper respiratory tract viral disorders (C?) Feline panleukopenia (C?) Feline infectious peritonitis (C?) Toxoplasmosis (C) Suppurative processes (D, C)

#### Neoplasia

Mast cell tumors (D, C) Lymphomas (D, C) Myeloproliferative disorders (C) Solid tumors (D, C)

#### Miscellaneous

Soft tissue trauma (D?, C?) Feline urologic syndrome (C?) Cardiomyopathy (D?, C?) Renal failure (D?, C?) Hyperthyroidism (C?) Estrus (D?)

Common; relatively common; uncommon; D, dog; C, cat; ?, poorly documented.

Eosinophilia can also occur in dogs and cats with mast cell tumors, but it is rare.

Clinical signs in dogs and cats with eosinophilia are related to the primary disorders rather than to the hematologic abnormality. Because eosinophilia is so commonly found in animals with parasitic diseases, clinical evaluation of these animals should be aimed mainly at excluding these disorders. Once this has been done, other causes of eosinophilia should be pursued (see Box 85-3) by using the appropriate diagnostic procedures (e.g., tracheal wash or pulmonary



#### Causes of Basophilia in Cats and Dogs

#### Disorders Associated with Immunoglobulin E Production and Binding

Heartwarm disease (D, C) Inhalant dermatitis [D, C]

#### Inflammatory Diseases

Gastrointestinal tract disease (D, C) Respiratory tract disease (D, C)

#### **Neoplasms**

Mast cell tumors (D, C) Lymphomatoid granulomatosis (D, C) Basophilic leukemia (D)

#### Associated with Hyperlipoproteinemia

Hypothyroidism (D?)

Common; relatively common; uncommon; D, dog; C, cat; ?, poorly documented.

fine-needle aspiration for pulmonary infiltrates with eosinophils, endoscopic biopsy for eosinophilic gastroenteritis). Treatment is usually aimed at the primary disorder.

A syndrome with high eosinophil counts in peripheral blood and tissue infiltration with eosinophils has been well documented in cats, Rottweilers, and occasionally other dog breeds. This syndrome is termed hypereosinophilic syndrome and is usually indistinguishable from eosinophilic leukemia. These patients have primary gastrointestinal tract signs, although multisystemic signs are also common. In cats, treatment with immunosuppressive doses of corticosteroids, 6-thioguanine, cytosine arabinoside, cyclophosphamide, and other anticancer agents (see Chapter 79) has been unrewarding, and most affected patients die within weeks of diagnosis. Clinical response to some of these drugs has been documented in Rottweilers.

#### BASOPHILIA

Basophilia is defined as an absolute increase in the basophil numbers and is commonly associated with eosinophilia. Because basophils are similar to tissue mast cells, their numbers increase in disorders characterized by excessive immunoglobulin E production and binding and in a variety of nonspecific inflammatory disorders. Causes of basophilia are listed in Box 85-4.

#### **MONOCYTOSIS**

Monocytosis refers to an absolute increase in monocyte numbers. It can occur in response to inflammatory, neoplastic, or degenerative stimuli. Although monocytosis has traditionally been observed primarily in chronic inflammatory processes, it is also common in acute disorders. Causes of monocytosis in cats and dogs are listed in Box 85-5. The



#### Causes of Monocytosis in Cats and Dogs

#### Inflammation

Infectious disorders

Bacteria

Pyometra (D, C)

Abscesses (D, C)

Peritonitis (D, C)

Pyothorax (D, C)

Osteomyelitis (D, C)

Prostatitis (D)

#### Higher bacteria

Nocardia (D, C)

Actinomyces (D, C)

Mycobacteria (D, C)

#### Intracellular parasites

Ehrlichia (D, C?)

Mycoplasma (D, C)

#### Fungi

Blastomyces (D, C)

Histoplasma (D, C)

Cryptococcus (D, C)

Coccidioides (D)

#### Parasites

Heartworms (D, C?)

#### Immune-mediated disorders

Hemolytic anemia (D, C)

Dermatitis (D, C)

Polyarthritis (D, C)

Trauma with Severe Crushing Injuries (D, C)
Hemorrhage into Tissues or Body Cavities (D, C)

Stress- or Corticosteroid-Induced Disorders (D)

#### Neoplasia

Associated with tumor necrosis (D, C)

Lymphoma (D, C)

Myelodysplastic disorders (D, C)

#### Leukemias

Myelomonocytic leukemia (D, C)

Monocytic leukemia (D, C)

Myelogenous leukemia (D, C)

**Common**; relatively common; uncommon; D, dog; C, cat; ?; poorly documented.

monocytosis in dogs is typically more pronounced than that in cats; monocytosis is extremely rare in Greyhounds.

Monocytosis is part of a stress leukogram in dogs. It can result from a variety of bacterial, fungal, and protozoal diseases. In the Midwest, systemic fungal disorders (e.g., histoplasmosis and blastomycosis) are relatively common causes.



#### Causes of Lymphopenia in Cats and Dogs

Corticosteroid or stress-induced disorders (D, C) (see Box 85-2)

Loss of Lymph

Lymphangiectasia (D, C) Chylothorax (D, C)

Impaired Lymphopoiesis

Chemotherapy (D, C)

Long-term corticosteroid use (D, C)

#### **Viral Diseases**

Parvoviruses (D, C)
Feline infectious peritonitis (C)
Feline leukemia virus (C)
Feline immunodeficiency virus (C)

Canine distemper (D)
Canine infectious hepatitis (D)

**Common**; relatively common; uncommon; D, dog; C, cat; ?, poorly documented.

Because monocytes are precursors of tissue macrophages, granulomatous and pyogranulomatous reactions commonly result in monocytosis (see Box 85-5). In addition, immunemediated injury resulting in cell destruction (e.g., immune hemolysis, polyarthritis) and certain neoplasms (e.g., lymphomas) may cause monocytosis. Some neoplasms secrete CSFs for monocytes and can result in marked monocytosis (more than  $5000/\mu L$ ).

The nature of the clinical evaluation in patients with monocytosis is similar to that used with neutrophilia: it should concentrate on identifying infectious foci. If an immune-mediated disorder is suspected, arthrocentesis to obtain fluid for analysis or other immune tests (see Chapter 92) should be performed. Treatment should be aimed at the primary disorder.

#### **LYMPHOPENIA**

Lymphopenia is defined as an absolute decrease in the lymphocyte count. It constitutes one of the most common hematologic abnormalities in hospitalized or sick dogs and cats, in which it is attributed to the effects of endogenous corticosteroids (stress leukogram). Lymphopenia is also commonly identified in dogs and cats with chronic loss of lymph, such as those with chylothorax or intestinal lymphangiectasia (Box 85-6).

In general, cats and dogs with lymphopenia have obvious clinical abnormalities. As a general rule, it should be "ignored" (i.e., a diagnosis should not be pursued) in sick cats and dogs and in those receiving corticosteroids. The lymphocyte count should be reevaluated after the clinical abnormalities have resolved or steroid therapy has been discontinued. Contrary to popular belief, lymphopenia does not appear to predispose to infection.



Causes of Lymphocytosis in Cats and Dogs

Physiologic or epinephrine-induced disorders (C) (see Box 85-2)

Prolonged Antigenic Stimulation
Chronic infection

Ehrlichiosis (D, C?) Chagas' disease (D) Babesiosis (D) Leishmaniasis (D)

Hypersensitivity reactions (?) Immune-mediated disease (?) Postvaccinal reaction (D, C) Leukemia

Lymphocytic (D, C)
Lymphoblastic (C, D)

Hypoadrenocorticism (D)

**Common;** relatively common; uncommon; D, dog; C, cat; ?, poorly documented.

#### LYMPHOCYTOSIS

Lymphocytosis is defined as an absolute increase in lymphocyte numbers. It is common in several clinical situations, including fear (cats; see Neutrophilia, above), vaccination (dogs and possibly cats), chronic ehrlichiosis (dogs), Addison's disease (hypoadrenocorticism; dogs), and chronic lymphocytic leukemia (CLL). The lymphocytes are morphologically normal in all these disorders, with the exception of vaccination reactions, in which reactive lymphocytes (larger cells with a dark blue cytoplasm) are commonly seen. High numbers of morphologically abnormal (i.e., blast) lymphoid cells are found in dogs and cats with acute lymphoblastic leukemia (see Chapter 81).

In cats with marked lymphocytosis and neutrophilia, endogenous release of catecholamines should be ruled out as the cause of these hematologic abnormalities. If the cat is fractious and blood cannot be collected without a considerable struggle, a blood sample should be collected under chemical restraint.

Recent vaccination should be ruled out in dogs with lymphocytosis and reactive lymphocytes in the blood smear. Most dogs with lymphocyte counts of more than 10,000 cells/µL have either chronic ehrlichiosis or CLL; most dogs with monocytic ehrlichiosis have increased numbers of large granule lymphocytes (LGL), larger lymphocytes with abundant cytoplasm, and large azurophilic cytoplasmic granules. LGL lymphocytosis can also occur in dogs with CLL. Lymphocyte counts of more than 20,000 cells/µL are extremely rare in dogs with ehrlichiosis (i.e., dogs with more than 20,000 lymphocytes/µL more likely have CLL). A high proportion of these dogs also has hyperproteinemia caused by

a monoclonal or polyclonal gammopathy (see Chapter 89). The clinical and hematologic features of monocytic ehrlichiosis and CLL are quite similar (e.g., cytopenia, hyperproteinemia, hepatosplenomegaly, lymphadenopathy). Serologic tests or polymerase chain reaction (PCR) testing for Ehrlichia canis, immunophenotyping of peripheral blood lymphocytes, PCR for clonality, and bone marrow aspiration findings may be helpful in differentiating these two disorders. Bone marrow cytologic findings in dogs with chronic ehrlichiosis usually consist of generalized hematopoietic hypoplasia and plasmacytosis, whereas hypoplasia with increased numbers of lymphocytes is more common in dogs with CLL. Causes of lymphocytosis in cats and dogs are listed in Box 85-7.

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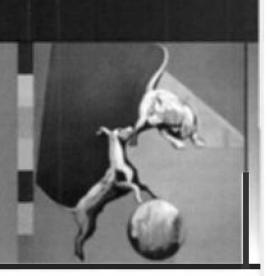
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## CHAPTER

# Combined Cytopenias and Leukoerythroblastosis



#### CHAPTER OUTLINE

DEFINITIONS AND CLASSIFICATION CLINICOPATHOLOGIC FEATURES

#### **DEFINITIONS AND CLASSIFICATION**

Combined cytopenias commonly result from decreased bone marrow production or, less frequently, from increased destruction or sequestration of circulating cells. Following are the definitions of several terms used throughout this chapter. Bicytopenia is a decrease in the numbers of two circulating blood cell lines (anemia and neutropenia, anemia and thrombocytopenia, or neutropenia and thrombocytopenia). If all three cell lines are affected (anemia, neutropenia, thrombocytopenia), this is called pancytopenia (from the Greek word pan, meaning "all"). In most cases, if anemia is present it is nonregenerative. If regenerative anemia occurs in association with other cytopenias, the cause usually is peripheral destruction of cells. Leukoerythroblastic reaction (LER) (or leukoerythroblastosis) refers to the presence of immature white blood cells (WBCs) and nucleated red blood cells (nRBCs) in the circulation (i.e., nRBCs and a left shift). In these cases the WBC count is usually high, but it can be normal or low.

As mentioned, cytopenias can develop as a result of decreased production or increased peripheral destruction of the affected cell line(s). In general, bicytopenias and pancytopenias result from primary bone marrow disorders (i.e., there is a problem in the "cell factory") (Box 86-1), although they may also result from peripheral blood cell destruction, such as what occurs in sepsis, disseminated intravascular coagulation (DIC), and some immune-mediated blood disorders.

LERs result from a variety of mechanisms (Box 86-2), but in general the presence of immature blood cells in the circulation is secondary to their premature release from the bone marrow or from other hematopoietic organs (spleen, liver). This premature release can result from (1) an increased demand for blood cells (e.g., hemolytic anemia, blood loss, peritonitis), resulting in a shorter transit time through the bone marrow compartments or extramedullary hematopoietic sites; or (2) the crowding out of normal bone marrow precursors (e.g., leukemia, bone marrow lymphoma). They may also be prematurely released from a site of extramedullary hematopoiesis (EMH) (i.e., spleen, liver) as a result of the absence of normal feedback mechanisms.

#### **CLINICOPATHOLOGIC FEATURES**

The clinical signs and physical examination findings in dogs and cats with combined cytopenias or LERs are usually related to the underlying disorder rather than the hematologic abnormalities per se, with the exception of pallor and spontaneous bleeding (petechiae, ecchymoses) secondary to anemia and thrombocytopenia, respectively. Pyrexia may be present if the patient is markedly neutropenic and is septic or bacteremic.

An important aspect of the clinical evaluation of these patients is the history. A detailed history should be obtained, with particular inquiries about the therapeutic use of drugs (e.g., estrogen or phenylbutazone in dogs, griseofulvin or chloramphenicol in cats), exposure to benzene derivatives (rare), travel history, vaccination status, and exposure to other animals, among others. Most drugs that cause anemia or neutropenia can also cause combined cytopenias (see Boxes 83-2 and 85-1).

The physical examination of dogs and cats with combined cytopenias may reveal the presence of spontaneous hemorrhages compatible with a primary hemostatic disorder (e.g., thrombocytopenia) or pallor secondary to the attendant anemia. Several physical examination findings may help the clinician establish a more presumptive or definitive diagnosis in patients with cytopenias or LER. Of particular interest is the finding of male-feminizing signs in a male dog (usually a cryptorchid) with pancytopenia, which may indicate the presence of a Sertoli cell tumor or, less frequently, an interstitial cell tumor or a seminoma with secondary hyperestrogenism. The finding of generalized



#### Causes of Bicytopenia and Pancytopenia in Dogs and Cats

#### Decreased cell production

#### Bone Marrow Hypoplasia-Aplasia

Idiopathic

Chemicals (e.g., benzene derivatives)

Estrogen (endogenous or exogenous)

Drugs (chemotherapeutic agents, antibiotics, anticonvulsants, colchicine, nonsteroidal antiinflammatories)

Radiation therapy

Immune-mediated disorders

**Infectious** (parvovirus, FeLV, feline immunodeficiency virus, *Ehrlichia canis*, and plasmosis)

#### **Bone Marrow Necrosis**

#### Infectious disorders (sepsis, parvovirus)

Toxins (mycotoxins)

Neoplasms (acute and chronic leukemias, metastatic neoplasia)

Other (hypoxia, DIC)

#### **Bone Marrow Fibrosis-Sclerosis**

Myelofibrosis Osteosclerosis

Osteopetrosis

#### Myelophthisis

Neoplasms

#### Acute leukemias

Chronic leukemias

Lymphoma

#### Multiple myeloma

Systemic mast cell disease

Malignant histiocytosis

Metastatic neoplasms

Granulomatous disorders

Histoplasma capsulatum

Mycobacterium spp.

Storage diseases

#### Myelodysplasia

#### Increased Cell Destruction and Sequestration Immune-Mediated Disorders

Evans syndrome

Sepsis

Microangiopathy

DIC

Hemangiosarcoma

#### **Splenomegaly**

Congestive splenomegaly

Hypersplenism

Hemolymphatic neoplasia

Other neoplasms

**Common**; relatively common; uncommon. DIC, Disseminated intravascular coagulation. FELV, Feline leukemia virus.



BOX 86-2

#### Causes of Leukoerythroblastosis in Dogs and Cats

#### EMH'

#### Immune hemolytic anemia

Blood loss anemia

Sepsis

DIC

Chronic hypoxia (i.e., congestive heart failure)

Neoplasia

#### Hemangiosarcoma

Lymphoma

Leukemias

Multiple myeloma

Other

Diabetes mellitus

**Hyperthyroidism** 

Hyperadrenocorticism

Common; relatively common; uncommon.

H may play a role in the pathogenesis of the LER in several of the

disorders mentioned in the text.

EMH, Extramedullary hematopoiesis; DIC, disseminated intravascular coagulation; LER, leukoerythroblastic reaction.

lymphadenopathy, hepatomegaly or splenomegaly, or intraabdominal or intrathoracic masses may direct the clinician toward a specific group of presumptive diagnoses. For example, the finding of a cranial or mid-abdominal mass in a dog with anemia, thrombocytopenia, and LER is highly suggestive of splenic hemangiosarcoma.

The presence of diffuse splenomegaly indicates that the spleen may be sequestering or destroying circulating blood cells or that EMH is occurring in response to a primary bone marrow disorder. Cytologic evaluation of spleen specimens obtained by percutaneous fine-needle aspiration is always indicated in dogs and cats with cytopenias and diffuse splenomegaly to determine whether the enlarged spleen is the cause or consequence of the cytopenia (see Chapter 88).

Serologic studies or polymerase chain reaction (PCR) for infectious diseases is usually indicated in dogs and cats with bicytopenias or pancytopenias. Infectious diseases associated with bicytopenias and pancytopenias commonly diagnosed on serologic PCR findings include monocytic ehrlichiosis in dogs, Babesia gibsoni infection in dogs (combined anemia and thrombocytopenia), and feline leukemia virus (FeLV) and feline immunodeficiency virus infections in cats. If the clinical and hematologic features of the case point toward an immune-mediated disease (e.g., presence of polyarthritis or proteinuria, spherocytosis) a direct Coombs' test and an antinuclear antibody test should be done (see Chapter 92). It is also helpful to submit fluid obtained from one or more joints for cytologic evaluation because the presence of suppurative nonseptic arthritis suggests an immune pathogenesis or a rickettsial disease.

Because establishing whether the cytopenia is the result of peripheral cell destruction or a bone marrow disorder is

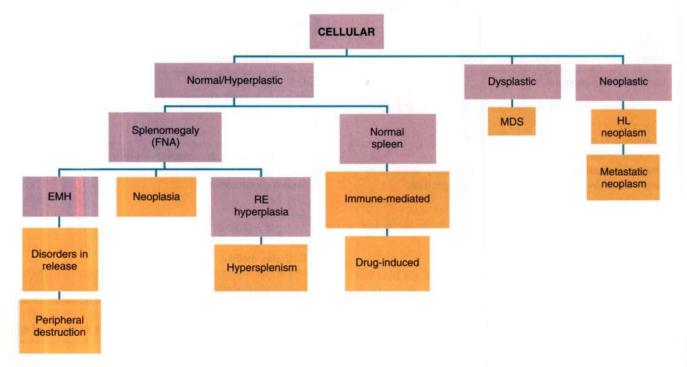


FIG 86-1
Algorithm for the diagnosis of a pancytopenic animal with hypercellular bone marrow.
FNA, Fine-needle aspiration; MDS, myelodysplastic syndrome; HL, hemolymphatic; EMH, extramedullary hematopoiesis; RE, reticuloendothelium. Orange boxes indicate final diagnoses.

important, evaluation of the "cell factory" is logical if no evidence of RBC regeneration in the blood smear or CBC exists (see Chapter 85). Therefore bone marrow aspiration and, ideally, bone marrow core biopsy to obtain specimens for histopathologic studies should be performed in all dogs and cats with combined cytopenias, except for dogs with highly likely or confirmed Evans syndrome and dogs and cats with DIC (i.e., the anemia is regenerative; thus it is assumed that the factory is working properly). Algorithms for the evaluation of bone marrow findings in dogs and cats with bicytopenia and pancytopenia are shown in Figs. 86-1 and 86-2. In private practice obtaining a bone marrow aspirate is usually easier; bone marrow core biopsies are usually performed at referral practices.

A bone marrow evaluation should also be part of the clinical workup in animals with LERs to determine whether the immature WBCs and RBCs in the circulation are secondary to a primary bone marrow disorder or a disorder such as EMH. Because abdominal neoplasms, particularly hemangiosarcoma, are commonly associated with LERs in dogs, abdominal ultrasonography should be done. If diffuse splenomegaly is detected, percutaneous fine-needle aspiration of the spleen should be performed. If splenic or hepatic masses or both are present, the patient should be evaluated as described in Chapter 90.

Weiss (2006) recently reviewed bone marrow aspirates, core biopsies, and medical records of 717 dogs evaluated for presumptive bone marrow disorders. Approximately 2% of

the specimens evaluated were nondiagnostic, 22% were normal, 26% had changes secondary to another primary disease, 24% had nondysplastic and nonneoplastic conditions, 9% had dysplasia, and 18% had neoplasia. Less than 5% of the specimens evaluated had bone marrow hypoplasia and approximately 20% were hyperplastic; acute leukemias were more common than chronic leukemias.

#### **Bone Marrow Aplasia-Hypoplasia**

Bone marrow aplasia-hypoplasia is a disorder characterized by peripheral blood cytopenias and a paucity or absence of hematopoietic precursors in the bone marrow. As previously discussed, bone marrow aplasia-hypoplasia is commonly associated with the administration of certain drugs, such as griseofulvin or chloramphenicol in cats and phenylbutazone or estrogen in dogs. It is also commonly associated with infectious diseases, such as canine monocytic ehrlichiosis and FeLV infection. A corticosteroid-responsive syndrome of combined cytopenias or pancytopenia has been recognized in dogs and cats in the author's clinic. Some patients with pancytopenia have hypercellular bone marrow (see below), suggesting that the cells are destroyed peripherally or at the late stages of bone marrow production.

Bone marrow aspirates from dogs and cats with bone marrow aplasia or hypoplasia typically show hypocellularity or acellularity, and a bone marrow biopsy is frequently necessary to obtain specimens for histopathologic analysis so that a definitive diagnosis can be made. Once infectious

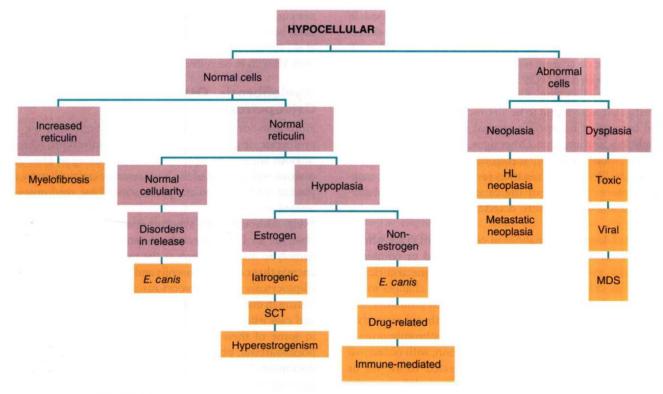


FIG 86-2
Algorithm for the diagnosis of a pancytopenic animal with hypocellular bone marrow. HL, Hemolymphatic; MDS, myelodysplastic syndrome; SCT, Sertoli cell tumor. Orange boxes indicate final diagnoses.

diseases (e.g., Ehrlichia canis titer, SNAP test [IDEXX, Westbrook, Maine], or PCR; FeLV p27 determination) and drug exposure have been ruled out, a therapeutic trial of immunosuppressive doses of corticosteroids (with or without other immunosuppressive drugs; see Chapter 93) may be warranted. Anabolic steroids and erythropoietin do not appear to be beneficial in these patients.

**Myelophthisis.** Infiltration of the bone marrow with neoplastic or inflammatory cells can lead to the crowding out of normal hematopoietic precursors and therefore the development of peripheral blood cytopenias. Disorders resulting in myelophthisis are listed in Box 86-1. Often these animals are evaluated because of anemia, although fever and bleeding caused by neutropenia and thrombocytopenia, respectively, can also be presenting complaints. The presence of hepatomegaly, splenomegaly, or lymphadenopathy in a dog or cat with anemia or combined cytopenias is highly suggestive of some of the neoplastic or infectious disorders listed in Box 86-1.

A definitive diagnosis in dogs and cats with myelophthisis is obtained by evaluating the cytologic or histopathologic characteristics of a bone marrow specimen. Given the fact that certain neoplastic or granulomatous disorders can show a patchy or multifocal distribution, the findings yielded by a bone marrow core biopsy specimen are usually more reliable than those yielded by an aspirate. Once a cytologic or histopathologic diagnosis is obtained, treatment is aimed at the

primary neoplasm (i.e., with chemotherapy) or infectious agent (see specific sections for detailed discussion).

#### Myelodysplastic Syndromes

Myelodysplastic syndromes include a host of hematologic and cytomorphologic changes that may precede the development of acute leukemias by months or years. In addition to the morphologic abnormalities in blood and bone marrow, functional abnormalities of granulocytes and platelets have been well documented in human beings with MDS. Therefore recurrent infections, spontaneous bleeding tendencies, or both are common in such patients, even when the neutrophil and platelet counts are within normal limits. These abnormalities have also been observed in cats with MDS.

MDS has been recognized in both dogs and cats but appears to be more common in retrovirus-infected cats. All dogs are lethargic, depressed, and anorectic. Physical examination findings include hepatosplenomegaly, pallor, and pyrexia; hematologic changes include pancytopenia or bicytopenia, macrocytosis, metarubricytosis, and reticulocytopenia. acute myelogenous leukemia (AML) subsequently developed 3 months after the initial diagnosis of MDS in one of the author's patients (Couto et al., 1984). The cytologic bone marrow abnormalities were similar to those described in cats and are discussed below. Some authors have proposed classifying dogs with primary myelodysplastic syndromes into those with refractory anemia and those with true myelo-

dysplasia, following similar classification schemes used in human beings (Weiss et al., 2000). However, because almost no clinical information was provided for the dogs evaluated, that classification scheme is of questionable clinical relevance.

Several reports of MDS in cats have appeared in the literature. More than 80% of cats in whom the FeLV status was investigated were found to be viremic. Most cats were evaluated because of nonspecific clinical signs such as lethargy, weight loss, and anorexia. Other signs, such as dyspnea, recurrent infections, and spontaneous bleeding, were observed in a few cats. Physical examination revealed hepatosplenomegaly in more than half of the cats; generalized lymphadenopathy and pyrexia were detected in approximately one third.

Hematologic abnormalities in cats with MDS are similar to those seen in dogs; they include isolated or combined cytopenias, macrocytosis, reticulocytopenia, metarubricytosis, and macrothrombocytosis. Morphologic changes in the bone marrow include a normal to increased cellularity, less than 30% blasts, an increased myeloid/erythroid ratio, dyserythropoiesis, dysmyelopoiesis, and dysthrombopoiesis. Megaloblastic RBC precursors are common, with occasional binucleated, trinucleated, or tetranucleated rubricytes or metarubricytes. The morphologic abnormalities in the myeloid cell line include giant metamyelocytes and asynchronous nuclear-cytoplasmic maturation.

Acute leukemia subsequently developed within weeks to months of the diagnosis in approximately one third of cats with MDS described in the literature. MDS commonly progresses to AML in human beings, with only isolated reports of progression to acute lymphocytic leukemia (ALL). However, according to Maggio and colleagues (1978), in one series of 12 cats with MDS, ALL subsequently developed in nine. This may reflect the fact that cytochemical staining was not done to classify the leukemic cells, and cells were thus morphologically classified as lymphoid when they were myeloid. However, because all the cats that showed progression to ALL were also viremic with FeLV, the hematologic changes preceding the development of leukemia did not reflect a "spontaneous" hematologic disorder (as seen in human beings and dogs) but were rather a manifestation of the morphologic and functional changes induced by FeLV.

The management of dogs and cats with MDS is still controversial. A variety of treatments have been used in human beings with MDS; however, none has proved effective. Chemotherapy, supportive therapy, anabolic steroids, inductors of differentiation, hematopoietic growth factors, and androgenic steroids, among others, have been reported to be of benefit in some human beings with MDS. Currently the preferred approach in human beings is treatment with supportive therapy and inductors of differentiation or hematopoietic growth factors. Because most patients are older, chemotherapy does not constitute the first treatment option, given its toxicity. The author recommends supportive therapy (e.g., fluids, blood components, antibiotics) and low-dose cytosine arabinoside as an inductor of differentiation (see Box 81-3). Aclarubicin (5 mg/m² IV q24h for 5 days), a drug

not currently available in the United States, was reported to be of benefit in a Shih Tzu with myelodysplasia (Miyamoto et al., 1999). Novel therapeutic approaches in human beings with MDS have been discussed by Warlick and Smith (2007).

# Myelofibrosis, Osteosclerosis, and Osteopetrosis

Fibroblasts or osteoblasts within the bone marrow can proliferate in response to retroviral infections, chronic noxious stimuli, or unknown causes, leading to fibrous or osseous replacement of the bone marrow cavity, thereby displacing the hematopoietic precursors. These syndromes are termed myelofibrosis and osteosclerosis-osteopetrosis, respectively. Although both syndromes are rare, they have been observed in FeLV-infected cats and in dogs with chronic hemolytic disorders, such as the pyruvate kinase deficiency anemia that occurs in Basenjis and Beagles. Peripheral blood elliptocytosis and dacryocytosis appear to be a common feature in dogs with myelofibrosis. A limited number of dogs and cats with idiopathic myelofibrosis have been reported; in some of these cases, previous exposure to drugs (e.g., phenobarbital, phenytoin, phenylbutazone, colchicine) was documented. In the author's experience, the clinical and hematologic features associated with myelofibrosis in dogs frequently resolve after immunosuppressive treatment with a combination of corticosteroids and azathioprine (see Chapter 93); the author has limited experience with myelofibrosis in FeLV-negative cats.

A presumptive diagnosis of osteosclerosis/osteopetrosis is made on the basis of the presence of combined cytopenias together with increased osseous radiographic density and can be confirmed by a core biopsy of the bone marrow. Unfortunately, no effective treatment is available.

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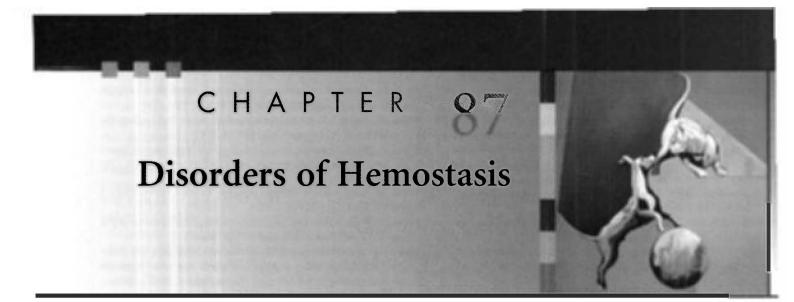
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#### CHAPTER OUTLINE

GENERAL CONSIDERATIONS PHYSIOLOGY OF HEMOSTASIS CLINICAL MANIFESTATIONS OF SPONTANEOUS **BLEEDING DISORDERS** CLINICOPATHOLOGIC EVALUATION OF THE **BLEEDING PATIENT** MANAGEMENT OF THE BLEEDING PATIENT PRIMARY HEMOSTATIC DEFECTS Thrombocytopenia Platelet Dysfunction SECONDARY HEMOSTATIC DEFECTS Congenital Clotting Factor Deficiencies Vitamin K Deficiency MIXED (COMBINED) HEMOSTATIC DEFECTS Disseminated Intravascular Coagulation THROMBOSIS

**GENERAL CONSIDERATIONS** 

Spontaneous or excessive bleeding is relatively common in small animals, particularly in dogs. As a general rule, a systemic hemostatic abnormality is the underlying cause of excessive bleeding in dogs and cats that have sustained trauma or are undergoing a surgical procedure and in dogs evaluated because of spontaneous bleeding tendencies (spontaneous bleeding is rare in cats with hemostatic abnormalities). Approaching these patients' bleeding in a logical and systematic fashion allows the clinician to confirm the presumptive diagnosis in most cases.

In addition to bleeding, abnormal hemostatic mechanisms can also cause thrombosis and thromboembolism, potentially leading to organ failure. Spontaneous bleeding disorders are extremely common in dogs evaluated at our clinic but are rare in cats. Thromboembolic disorders are rare in both dogs and cats without underlying cardiovascular disorders (e.g., cats with hypertrophic cardiomyopathy and

aortic thromboembolism; see Chapter 12). The most common disorder leading spontaneous bleeding in dogs seen at our clinic is thrombocytopenia, mainly of immune-mediated pathogenesis. Other common hemostatic disorders leading to spontaneous bleeding in dogs evaluated at our hospital include disseminated intravascular coagulation (DIC) and rodenticide poisoning. Congenital clotting factor deficiencies resulting in spontaneous bleeding are rare. Although von Willebrand disease (vWD) is common in certain breeds (see p. 1251), it is not a common cause of spontaneous bleeding. Abnormalities in hemostasis screens are frequently noted in cats with liver disease, feline infectious peritonitis (FIP), or neoplasia; however, spontaneous bleeding tendencies are extremely rare in these patients. Decreased production of platelets (thrombocytopenia) or virus-induced thrombocytopathia resulting in spontaneous bleeding is occasionally seen in cats with retrovirus-induced bone marrow disorders.

#### PHYSIOLOGY OF HEMOSTASIS

Under normal conditions, injury to a blood vessel leads to immediate vascular changes (e.g., vasoconstriction) and rapid activation of the hemostatic system. Changes in axial blood flow lead to exposure of circulating blood to subendothelial collagen, resulting in rapid adhesion of platelets to the affected area. The adhesion of platelets to the subendothelium is mediated by adhesive proteins, such as von Willebrand factor (vWF) and fibrinogen. After adhering to the area of endothelial damage, platelets aggregate and form the *primary hemostatic plug*, which is short lived (seconds) and unstable. The primary hemostatic plug serves as a framework in which secondary hemostasis occurs because most of the clotting factors "assemble" the thrombus or clot on the platelet plug.

Although the intrinsic, extrinsic, and common coagulation pathways have been well characterized and are still used to teach physiology of hemostasis, coagulation in vivo does not necessarily follow these distinct pathways. For example, factors XII and XI do not appear to be necessary for the

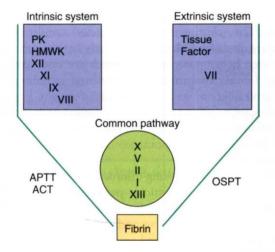


FIG 87-1
The traditional intrinsic, extrinsic, and common coagulation pathways. PK, Prekallikrein; HMWK, high-molecular-weight kininogen; APTT, activated partial thromboplastin time; ACT, activated coagulation time; OSPT, one-stage prothrom bin time.

initiation of coagulation (e.g., dogs and cats with factor XII deficiency do not have spontaneous bleeding tendencies). In the past 2 decades the traditional coagulation cascade has been thought of as a common pathway from early in the process; the traditional intrinsic, extrinsic, and common pathways are now known to be interrelated (Schenone et al., 2004)

In the traditional scheme, activation of the contact phase of the coagulation cascade occurs almost simultaneously with platelet adhesion and aggregation (Fig. 87-1) and leads to the formation of fibrin through the intrinsic coagulation cascade. A good mnemonic is to refer to the intrinsic system as the "dime store" coagulation cascade: "it is not \$12, but \$11.98" (for factors XII, XI, IX, and VIII). Factor XII is activated by contact with the subendothelial collagen and by the platelet plug; once it has been activated, fibrin, or the secondary hemostatic plug, forms. Prekallikrein (Fletcher factor) and high-molecular-weight kiningeen are important cofactors for factor XII activation. The role of the contact phase of coagulation in vivo is questionable. The secondary hemostatic plug is stable and long lasting. In addition, whenever tissue trauma occurs, the release of tissue procoagulants (collectively referred to as tissue factor) results in activation of the extrinsic coagulation cascade, also leading to the formation of fibrin (see Fig. 87-1). Tissue factor is ubiquitous and is present on the membrane of most cells, with the exception of normal endothelium.

The stimuli that activate the contact phase of coagulation also activate the fibrinolytic and kinin pathways. Fibrinolysis is extremely important as a safeguard mechanism because it prevents excessive clot or thrombus formation. When plasmin lyses fibrinogen and fibrin, it generates fibrin degradation products (FDPs), which impair additional platelet adhesion and aggregation in the site of injury. Once fibrin

has been stabilized by complexing factor XIII, plasmin biodegradation generates D-dimers instead. The activation of plasminogen into plasmin results in the destruction (lysis) of an existing clot (or thrombus) and interferes with the normal clotting mechanisms (inhibition of platelet aggregation and clotting factor activation in the affected area). Therefore excessive fibrinolysis usually leads to spontaneous bleeding. Two molecules stimulate plasminogen activation into plasmin: tissue plasminogen activator (tPA) and urokinase-type plasminogen activator. Three plasminogen activator inhibitors (PAI) termed PAI-1, -2, and -3 inhibit fibrinolysis, thus leading to thrombosis.

Other systems that oppose blood coagulation also become operational once intravascular clotting has occurred. The best-characterized ones include antithrombin (AT), a protein synthesized by hepatocytes that acts as a co-factor for heparin and inhibits the activation of factors IX, X, and thrombin. AT also inhibits tPA. Proteins C and S are two vitamin K–dependent anticoagulants also produced by hepatocytes. These three factors are some of the natural anticoagulants that prevent excessive clot formation.

#### CLINICAL MANIFESTATIONS OF SPONTANEOUS BLEEDING DISORDERS

In the evaluation of a cat or dog with spontaneous or excessive bleeding, the clinician should ask the owners the following questions, which may provide additional clues to the pathogenesis of the coagulopathy:

- Is this the first bleeding episode? If it is occurring in a mature animal, an acquired coagulopathy is suspected.
- Has the animal had any surgeries before this and, if so, did it bleed excessively? If the pet has had previous bleeding episodes during elective surgeries, a congenital coagulopathy is suspected.
- Do any litter mates have similar clinical signs? Did the litter have an increased perinatal mortality rate? These findings also support a congenital coagulopathy.
- Has the animal recently been vaccinated with modified-live vaccines? Modified-live vaccines can cause thrombocytopenia, platelet dysfunction, or both.
- Is the animal currently receiving any medication that may cause thrombocytopenia or platelet dysfunction (e.g., nonsteroidal antiinflammatories [NSAIDs], sulfas, antibiotics, phenobarbital)?
- Does the animal have access to rodenticides or does it roam freely? This may indicate rodenticide toxicity.

The clinical manifestations of primary hemostatic abnormalities are quite different from those of secondary hemostatic abnormalities (Box 87-1). Indeed, the clinician should be able to classify the type of coagulopathy on the basis of the physical examination findings before submitting any samples for laboratory evaluation. This is rather easy to



BOX 87-1

Clinical Manifestations of Primary and Secondary Hemostatic Defects

#### **Primary Hemostatic Defect**

#### Petechiae common Hematomas rare Bleeding in skin and mucous membranes Bleeding immediately after venipuncture

#### **Secondary Hemostatic Defect**

Petechiae rare
Hematomas common
Bleeding into muscles, joints,
and body cavities
Delayed bleeding after
venipuncture

conceptualize by thinking about the normal coagulation mechanisms. For example, a primary hemostatic plug cannot form in a cat or dog with severe thrombocytopenia or platelet dysfunction. Because this plug is short lived and eventually covered with fibrin (generated through the secondary hemostatic mechanisms), multiple, short-lived bleeds occur that are arrested as soon as fibrin is formed, resulting in multiple small and superficial hemorrhages. This is analogous to turning on and off a faucet connected to a garden hose with multiple perforations (i.e., an irrigator); multiple spurts of water (i.e., blood) form adjacent to the hose (i.e., the vessel). On the other hand, a short-lived primary hemostatic plug can form in a cat or dog with severe clotting factor deficiencies (e.g., hemophilia, rodenticide poisoning); enough functional platelets are present, but fibrin cannot be generated. The result of this is a delayed, continuous, longlasting bleed, leading to hematoma formation or bleeding into a body cavity. This is analogous to turning on a faucet connected to a regular garden hose with a single large opening; in this situation, water (i.e., blood) continues to flow and collect in large amounts next to the opening in the hose (i.e., vessel).

Spontaneous bleeding infrequently occurs in cats and dogs with excessive fibrinolysis. I have evaluated four dogs with protein-losing nephropathy and nephrotic syndrome in which spontaneous bleeding (i.e., petechiae and ecchymoses) appeared to result from enhanced fibrinolysis. We have recently documented delayed postoperative bleeding in retired racing Greyhounds that may be associated with hyperfibrinolysis (Lara et al., 2007).

Cats and dogs with primary hemostatic defects (i.e., platelet disorders) therefore have typical manifestations of superficial bleeding, consisting of petechiae, ecchymoses, bleeding from mucosal surfaces (e.g., melena, hematochezia, epistaxis, hematuria), and prolonged bleeding immediately after venipuncture. In clinical practice, the majority of primary hemostatic disorders are caused by decreased numbers of circulating platelets (thrombocytopenia). Primary hemostatic defects occasionally result from platelet dysfunction (e.g., uremia, von Willebrand disease [vWD], monoclonal gammopathies, vector-borne diseases). Primary hemostatic defects caused by vascular disorders are extremely rare in cats and dogs and are not discussed here.

Clinical signs in cats and dogs with secondary hemostatic defects (i.e., clotting factor deficiencies) consist of deep bleeding, including bleeding into body cavities and joints, and deep hematomas, most of which are discovered as a lump. Certain congenital coagulopathies, including factor XII, prekallikrein, and high-molecular-weight kininogen deficiencies, result in a marked prolongation of the activated coagulation time (ACT) or activated partial thromboplastin time (APTT) without spontaneous or prolonged bleeding (see below).

Most secondary bleeding disorders seen in clinical practice are caused by rodenticide poisoning or liver disease; selective congenital clotting factor deficiencies occasionally can lead to spontaneous secondary bleeding disorders. A combination of primary and secondary bleeding disorders (mixed disorders) is seen almost exclusively in dogs and cats with DIC.

#### CLINICOPATHOLOGIC EVALUATION OF THE BLEEDING PATIENT

Clinicopathologic evaluation of the hemostatic system is indicated primarily in two subsets of patients: in those with spontaneous or prolonged bleeding and before surgery in patients with disorders commonly associated with bleeding tendencies (e.g., splenic hemangiosarcoma [HSA] and DIC in dogs; liver disease and clotting factor deficiency) or a suspected congenital coagulopathy (e.g., before ovariohysterectomy in a Doberman Pinscher suspected of having subclinical vWD).

When evaluating a cat or dog with a spontaneous bleeding disorder, the clinician should keep in mind that the preliminary clinical diagnosis can usually be confirmed by performing a handful of simple cage-side tests. If these tests do not yield a definitive answer or if a more specific diagnosis is desirable (e.g., the identification of specific clotting factor deficiencies), a plasma sample can be submitted to a referral veterinary diagnostic laboratory or a specialized coagulation laboratory (e.g., New York State Diagnostic Laboratory, Cornell University, Ithaca).

Some simple cage-side tests include evaluation of a blood smear; determination of the ACT, one-stage prothrombin time (OSPT), and APTT; quantification of FDP concentration or D-dimer assays; and the buccal mucosa bleeding time (BMBT) (Table 87-1). Examination of a good-quality, well-stained blood smear (e.g., Diff-Quik, Medion GmbH, Düdingen, Switzerland) provides important clues regarding platelet numbers and morphology. The first aspect of this examination should be to scan the smear at low power to identify platelet clumps; platelet clumping commonly results in pseudothrombocytopenia. Next, the oil immersion lens should be used to examine several representative monolayer fields (i.e., where approximately 50% of the red blood cells [RBCs] touch each other), and the number of platelets in five fields should be averaged. In dogs, 12 to 15 platelets should be present in each oil immersion field; in normal cats,



TABLE 87-1

Simple Cage-Side Tests for the Rapid Classification of Hemostatic Disorders

TEST	RESULTS	MOST LIKELY DISORDER(S) IF PROLONGED (OR POSITIVE)
Platelet estimation in blood smear	low	Thrombocytopenia
ACT	Prolonged	Intrinsic/common system defect
FDP/D-dimer	Positive	Enhanced fibrinolysis; DIC
BMBT	Prolonged	Thrombocytopenia, thrombocytopathia

ACT, Activated clotting time; FDP, fibrin degradation products; DIC, disseminated intravascular coagulation; BMBT, buccal mucosal bleeding



TABLE 87-2

#### Interpretation of Hemostasis Screens

DISORDER	ВТ	ACT	OSPT*	АРТТ	PLATELETS	FIBRINOGEN	FDPs
Thrombocytopenia	<b>↑</b>	Ν	N	N	$\downarrow$	Ν	Ν
Thrombocytopathia	<b>↑</b>	Ν	Ν	Ν	Ν	N	Ν
vWD ′	1	N∖ţŝ	Ν	N∖Ţŝ	Ν	Ν	Ν
Hemophilias	N	<b>↑</b>	Ν	<u>↑</u>	Ν	Ν	Ν
Rodenticide toxicity	N∖Ţŝ	1	1	$\uparrow$	N/↓	N/↓	N/↑
DIC	↑ ·	1	<b>↑</b>	<b>↑</b>	↓ .	N/↓	<b>↑</b>
Liver disease	N/↑	<b>↑</b>	N/T	<b>↑</b>	N/↓	N/↓	N

<sup>\*</sup>OSPT and APTT are considered prolonged if they are 25% or more than the concurrent controls.

10 to 12 platelets per field should be seen. As a general rule, each platelet in an oil immersion field represents 12,000 to 15,000 platelets/ $\mu$ L (i.e., number of platelets/oil immersion field  $\times$  15,000 = platelets/ $\mu$ L). Cats and dogs with platelet counts of more than 30,000/ $\mu$ L and normal platelet function do not bleed spontaneously. Therefore the cause of bleeding is usually not thrombocytopenia if more than two or three platelets are visualized in each oil immersion field. The evaluation of platelet numbers should also include evaluation of the morphology of individual platelets because abnormal platelet morphology may reflect impaired platelet function.

The second set of cage-side tests of hemostatic ability are the ACT, OSPT, and APTT. For the APTT, 2 mL of whole fresh blood is added to a tube containing diatomaceous earth; this activates the contact phase of coagulation, thus assessing the integrity of the intrinsic and common pathways (factors XII, XI, IX, VIII, X, V, II, and I) (see Fig. 87-1). If the activity of individual clotting factors involved in these pathways has decreased by more than 70% to 75%, the ACT is prolonged (normal, 60 to 90 seconds). Common coagulopathies associated with prolongation of the ACT are listed in Table 87-2. A cage-side instrument has recently been validated in dogs and cats (SCA 2000, Synbiotics Corp., San Diego, Calif.); a new easy-to-use instrument is now commercially available (CoagDx Analyzer, IDEXX, Westbrook,

Maine). These units perform evaluation of the APTT or OSPT with only a small volume of blood for each test. The reference ranges for the APTT with this instrument are different than for the APTT obtained in referral diagnostic laboratories.

The third cage-side test that can be easily performed in practice is the determination of the FDP concentration (or titer) with the commercially available Thrombo Wellcotest (Thermo Fisher Scientific, Lenexa, Kan.). This latex agglutination test can detect circulating FDPs, which are generated during the cleavage of fibrin and fibrinogen (i.e., fibrinolysis). This test is commonly positive in dogs and in some cats with DIC. The FDP test is also positive in more than half of dogs with bleeding caused by rodenticide poisoning (e.g., warfarin). The mechanism of the latter is unknown; however, these results cannot be reproduced by the intracavitary or intramuscular injection of anticoagulated blood in normal dogs. Vitamin K antagonists are believed to activate fibrinolysis by inhibiting the production of PAI-1. Recently a pointof-care D-dimer assay has been validated in the dog (Stokol, 2003).

A fourth cage-side test that can be performed primarily in dogs is the BMBT (Box 87-2), in which a template (Sim-Plate, IDEXX) is used to make an incision in the buccal mucosa and the time until bleeding completely ceases is

BT, Bleeding time; ACT, activated coagulation test; OSPT, one-stage prothrombin time; APTT, activated partial thromboplastin time; FDPs, fibrin degradation products; vWD, von Willebrand disease; DIC, disseminated intravascular coagulation; ↑, high or prolonged; N, normal or negative; ↓, decreased or shortened; ₹, questionable.



BOX 87-2

#### Procedure for Determining the BMBT in Dogs

- Position the animal in lateral recumbency with manual restraint.
- Place a 5-cm wide strip of gauze around the maxilla to fold up the upper lip, causing moderate engorgement of the mucosal surface.
- Position the SimPlate against the upper lip mucosa and push the trigger.
- 4. Start a stopwatch when the incisions are made.
- 8fot the blood with a gauze or blotting paper placed 1 to 3 mm ventral to the incision without dislodging the clot
- 6. Stop the stopwatch when the incision ceases to bleed.
- 7. Normal times are 2 to 3 minutes.

BMBT, Buccal mucosal bleeding time.

determined. The BMBT is abnormal in cats and dogs with thrombocytopenia or with platelet dysfunction. In an animal with clinical signs of a primary bleeding disorder (e.g., petechiae, ecchymoses, mucosal bleeding) and a normal platelet count, a prolonged bleeding time indicates an underlying platelet dysfunction (e.g., resulting from NSAID therapy or vWD) or, less likely, a vasculopathy. Unfortunately, the BMBT has high interoperator and intraoperator variability (as high as 80%), and the results are not reproducible, even by the same operator. The PFA-100 (see below) has replaced the BMBT in most veterinary teaching hospitals.

By performing these simple tests after evaluating the clinical features of the bleeding disorder, the clinician should be able to narrow down the number of differential diagnoses. For example, the blood smear evaluation reveals whether the patient is thrombocytopenic. If the patient is not thrombocytopenic but petechiae and ecchymoses are present, a prolonged bleeding time supports the existence of a platelet function defect. A prolonged ACT or APTT indicates that an abnormality in the intrinsic or common pathways; a prolonged OSPT documents a defect in the extrinsic pathway (i.e., factor VII); and a positive test result for FDPs supports the presence of primary or secondary fibrinolysis.

If further confirmation of a presumptive diagnosis is required, plasma can be submitted to a referral laboratory or a specialized coagulation laboratory (see p. 1244). Most commercial veterinary diagnostic laboratories routinely evaluate hemostatic profiles. Samples should be submitted in a purple-topped tube (sodium ethylene diamine tetraacetic acid) for platelet count, a blue-topped tube (sodium citrate) for coagulation studies (OSPT, APTT, fibrinogen concentration), and a special blue-topped tube (Thrombo Wellcotest) for FDP determination (the last tube is usually supplied by the diagnostic laboratory). The blue-topped tubes are now available in two different sodium citrate concentrations: 3.2% and 3.8%. The results of routine hemostasis assays are not affected by the concentration of citrate used



TABLE 87-3

Specimens Required for Laboratory Evaluation of Hemostasis

SAMPLE	TUBE TOP	TEST(S)
EDTA blood Citrated blood	Purple Blue	Platelet count OSPT, APTT, fibrinogen, AT, vWF, clotting factor assays, D-dimer, TEG, PFA-100
Thrombin	Blue	FDPs

EDTA, Ethylenediamine tetraacetic acid; OSPT, one-stage prothrombin time; APTT, activated partial thromboplastin time; AT, antithrombin, vWF, von Willebrand factor assay; TEG, Thromboelastograph; PFA-100, platelet function analyzer; FDP, fibrin degradation product.

(Morales et al., 2007). It is important to submit the right samples in the appropriate anticoagulant. The guidelines for sample submission to commercial laboratories are summarized in Table 87-3.

A routine coagulation screen (or hemostatic profile) usually contains the OSPT, APTT, platelet count, fibrinogen concentration, and FDP concentration (or titer). In some laboratories a D-dimer test and AT activity may also be included. The OSPT primarily evaluates the extrinsic pathway, whereas the APTT primarily evaluates the intrinsic pathway. Because the end product in these assays is always fibrin formation, both tests also evaluate the common pathway (see Fig. 87-1). The D-dimer assay evaluates for systemic fibrinolysis, as does the FDP test; however, the D-dimer is formed after fibrin as been stabilized by factor XIII. Thus it is more indicative of intravascular thrombus formation. The interpretation of routine hemostasis profiles is summarized in Table 87-2.

New instruments now allow evaluation of other aspects of hemostasis. For example, the platelet function analyzer PFA-100 (Siemens Healthcare Diagnostics, Deerfield, Ill.) is a simple, cage-side instrument to evaluate platelet adhesion and aggregation (Couto et al., 2006). This instrument is available in several specialized clinical hemostasis laboratories and has been extensively evaluated in dogs. The PFA-100 is quite sensitive in the diagnosis of vWD. The Thromboelastograph (TEG; Haemoscope, Niles, Ill.), also available in some specialized hemostasis laboratories, uses native or anticoagulated blood that is activated with a variety of agonists. This instruments evaluates global hemostasis, including platelet adhesion and aggregation, fibrin formation, fibrinolysis, and clot retraction. The TEG is ideal to monitor response to blood component therapy in patients with coagulopathies. I have found it to provide a wealth of information in patients with hypercoagulability and those with spontaneous bleeding and normal results of hemostasis profiles.



BOX 87-3

Congenital and Acquired Clotting Factor Defects

#### **Congenital Clotting Factor Defects**

Factor I, or hypofibrinogenemia and dysfibrinogenemia (St. Bernards and Borzois)

Factor II, or hypoprothrombinemia (Boxers, Otterhounds, English Cocker Spaniels)

Factor VII, or hypoproconvertinemia (Beagles, Malamutes, Boxers, Bulldogs, Miniature Schnauzers)

Factor VIII, or hemophilia A (many breeds but mainly German Shepherd dogs)

Factor IX, or hemophilia B (many breeds of dogs; domestic short-haired and British Shorthair cats)

Factor X, or Stuart-Prower trait (Cocker Spaniels, Jack Russell Terriers)

Factor XI, or hemophilia C (English Springer Spaniels, Great Pyrenees, Kerry Blue Terriers)

Factor XII, or Hageman factor (Miniature and Standard Poodles, Shar-Peis, German Shorthair Pointers; cats)

Prekallikrein (Fletcher factor) deficiency (various dog breeds

#### **Acquired Clotting Factor Defects** Liver disease

Decreased production of factors Qualitative disorders? Cholestasis

Vitamin K antagonists (rodenticides)

DIC, Disseminated intravascular coagulation.

As previously discussed, if an unusual coagulopathy or a specific clotting factor deficiency is suspected, blood should be submitted to a specialized veterinary coagulation laboratory (see p. 1244). Congenital and acquired clotting factor deficiencies that occur in cats and dogs are listed in Box 87-3.

Thrombocytopenia can be from either decreased production or increased destruction, consumption, or sequestration of platelets; therefore a bone marrow aspiration for cytologic evaluation is indicated in cats and dogs with thrombocytopenia of unknown cause. Other tests can also be performed in thrombocytopenic cats and dogs, including determinations of titers or polymerase chain reaction (PCR) for tickborne diseases, evaluation for retrovirus infection, radioactive platelet scanning, and antiplatelet antibody tests (see p. 1250).

Finally, clinicians occasionally encounter a patient with abnormal results of hemostasis profiles but without spontaneous bleeding. The most common "abnormality" in the hemostasis profile of a dog or cat without a tendency to bleed is a prolongation of the APTT. Quite frequently the prolongation is marked (more than 50% above the control or upper limit of the reference range for the laboratory). If this "abnormality" is found during a presurgical evaluation, the surgery

may be delayed needlessly if the clinician is not familiar with some of the following clinical conditions. As previously discussed, dogs and cats with factor XII deficiency do not bleed, yet they have a prolonged APTT; determination of factor XII activity will resolve this issue. Prekallikrein and high-molecular-weight kininogen (HMWK) are co-factors for contact activation of factor XII. Dogs with prekallikrein or HMWK deficiencies have prolonged APTT but do not bleed; incubation of the plasma samples for a few hours overrides the factor deficiency and corrects the APTT. Finally, the presence of circulating anticoagulants, also referred to as lupus anticoagulants, results in prolongation of the APTT without bleeding. A simple test to determine if the patient with a prolonged APTT has a clotting factor deficiency (e.g., factor XII) or circulating anticoagulants is to perform an APTT after diluting the patient's sample 50:50 with normal or pooled dog plasma (dilution assay). As previously discussed, the APTT becomes prolonged when the patient has less than 30% activity of an individual factor. If the patient has factor XII deficiency, for example, and 0% factor XII activity, mixing the sample 50:50 with normal dog plasma (with a factor XII activity of 100%), will result in a final factor XII activity of 50% and thus the APTT will be normal. Circulating anticoagulants also inhibit the clotting factors in the normal dog plasma, so when the samples are mixed 50:50 the APTT remains prolonged.

#### MANAGEMENT OF THE BLEEDING PATIENT

Several basic principles apply to the management of cats and dogs with spontaneous bleeding disorders. Specific principles are discussed in the following paragraphs. In general, a cat or dog with a spontaneous bleeding disorder should be managed aggressively because these disorders are potentially life threatening, but iatrogenic bleeding should be minimized. As a general rule, trauma should be minimized and the patient must be kept quiet, preferably confined to a cage and leash walked, if necessary. Exercise should be avoided or markedly restricted.

Venipunctures should be done with the smallest gauge needle possible, and pressure should be applied to the puncture site for a minimum of 5 minutes. A compressive bandage should also be applied to the area once pressure has been released. If repeated samples for packed cell volumes (PCVs) and plasma protein determinations are necessary, they should be obtained from a peripheral vein with a 25-gauge needle to fill one or two microhematocrit tubes by capillarity. A bandage should be applied after each venipuncture.

Invasive procedures should be minimized. For example, urine samples should never be collected by cystocentesis because of the risk of intraabdominal, intravesical, or intramural bladder bleeding. Certain invasive procedures, however, can be performed quite safely. These include bone marrow aspiration from the iliac crest or wing of the ilium,

fine-needle aspiration of lymph nodes or superficial masses, fine-needle aspiration of the spleen (the thick fibromuscular capsule of the carnivore spleen seals the needle hole as soon as the needle is removed), and intravenous catheter placement (although seepage from the catheter is common in thrombocytopenic patients).

Certain types of surgery can also be safely performed in some cats and dogs with coagulopathies. For example, pedicle surgery (e.g., splenectomy) can be performed with minimal bleeding (i.e., seepage from the abdominal wound) in dogs with marked thrombocytopenia (i.e., less than 25,000 platelets/ $\mu$ L).

A transfusion of blood or blood components is indicated in some dogs and cats with spontaneous bleeding disorders. Whole fresh blood (or a combination of packed RBCs and fresh frozen plasma) should be used if the animal is anemic and lacking one or more clotting factors; plasma transfusions are of no benefit in thrombocytopenic animals. Fresh frozen plasma can be used to replenish clotting factors in a cat or dog with a normal or mildly decreased packed cell volume (i.e., the animal is not symptomatic). Stored blood or frozen plasma is deficient in factors V and VIII. In general, whole fresh blood, platelet-rich plasma, and platelet transfusions rarely provide sufficient platelets to halt spontaneous bleeding in a cat or dog with thrombocytopenia, particularly if the bleeding is the result of platelet consumption. (Some guidelines for transfusion therapy are discussed in Chapter 83.)

#### PRIMARY HEMOSTATIC DEFECTS

Primary hemostatic defects are characterized by the presence of superficial and mucosal bleeding (e.g., petechiae, ecchymoses, hematuria, epistaxis) and are usually associated with thrombocytopenia. Platelet dysfunction is a rare cause of spontaneous bleeding in dogs and cats. Primary hemostatic defects caused by vascular problems are extremely rare and thus are not discussed here. Primary hemostatic defects are the most common cause of spontaneous bleeding in dogs seen at our hospital.

#### **THROMBOCYTOPENIA**

Thrombocytopenia represents the most common cause of spontaneous bleeding in dogs seen at our clinic. Decreased numbers of circulating platelets can be the result of one or more of the following abnormalities (Box 87-4):

- Decreased platelet production
- · Increased platelet destruction
- · Increased platelet consumption
- Increased platelet sequestration

Increased platelet destruction represents the most common cause of thrombocytopenia in dogs in our clinic, but it is rare in cats. Most commonly the peripheral destruction of platelets results from immune-mediated, drug-related



Causes of Thrombocytopenia in Dogs and Cats

#### **Decreased Platelet Production**

Immune-mediated megakaryocytic hypoplasia Idiopathic bone marrow aplasia

Drug-induced megakaryocytic hypoplasia (estrogens, phenylbutazone, melphalan, lomustine β-lactams)
Myelophthisis

Cyclic thrombocytopenia
Retroviral infection
Canine monocytic ehrlichiosis
Feline monocytic ehrlichiosis?

Increased Platelet Destruction, Sequestration, or Utilization

IMT

Infectious (Anaplasma spp., Bartonella spp., sepsis, etc.)
Live viral vaccine-induced thrombocytopenia

Drug-induced thrombocytopenia

Microangiopathy

DIC

Hemolytic uremic syndrome/thrombotic thrombocytopenic purpura

Vasculitis

Splenomegaly

Splenic torsion

Endotoxemia

Acute hepatic necrosis

Neoplasia (immune mediated, microangiopathy)

Common; relatively common; rare.

IMT, Immune-mediated thrombocytopenia; DIC, disseminated intravascular coagulation.

(including vaccination with modified-live viruses), and sepsis-related (see Box 87-4) mechanisms. Increased platelet consumption occurs most commonly in dogs and cats with DIC (see below), and sequestration is usually caused by splenomegaly or, rarely, hepatomegaly (see Box 87-4).

# Approach to the Patient with Thrombocytopenia

Before assessing a patient with primary hemostatic bleeding, the clinician must remember than in some breeds platelet counts below the reference range for dogs are common. Platelet counts in Greyhounds typically range between 80,000 and 120,000/µL, whereas in Cavalier King Charles Spaniels with macrothrombocytopenia platelet counts <50,000/µL are common. In the latter the global platelet function is normal. Once thrombocytopenia has been confirmed by a platelet count or evaluation of a blood smear, its pathogenesis should be identified. The absolute platelet count may offer clues to its cause; for example, platelet counts of less than 25,000/µL are common in dogs with immune-mediated thrombocytopenia (IMT), whereas

platelet counts of 50,000 to 75,000// $\mu$ L are more common in dogs with ehrlichiosis, lymphoma affecting the spleen, or rodenticide toxicity.

The patient's drug history should be obtained from the owner. If the animal is receiving any medication, the thrombocytopenia should be considered drug related until proven otherwise. The drug should be discontinued if possible and the platelet count reevaluated within 2 to 6 days. If the count returns to normal, a retrospective diagnosis of drug-associated thrombocytopenia is made. Drugs that have been associated with thrombocytopenia in cats and dogs can also cause anemia and neutropenia (see Boxes 83-2 and 85-1).

Because retroviral disorders commonly affect the bone marrow and may result in thrombocytopenia in cats, bone marrow aspiration is indicated in a thrombocytopenic cat with no history of previous medication. The risk of bleeding during or after bone marrow aspiration in a thrombocytopenic animal is minimal. Feline leukemia virus (FeLV) and feline immunodeficiency virus tests should also be performed. If determined by the laboratory, a mean platelet volume is high in most cats with FeLV infection (i.e., macrothrombocytosis); however, macrothrombocytes are also seen in cats and dogs with peripheral platelet destruction, consumption, or sequestration, in which they may be analogous to reticulocytes (young, immature, large platelets).

Bone marrow evaluation may also be indicated in dogs with thrombocytopenia. Given the high prevalence of IMT, at our clinic we usually elect to treat a dog with a presumed diagnosis of IMT. If the patient does not respond to immunosuppressive drugs within 2 to 3 days, a bone marrow aspiration may be performed.

Hyperplasia of megakaryocytes occurs in response to peripheral destruction, consumption, or sequestration of platelets. Occasionally dogs and cats with IMT have decreased numbers of megakaryocytes and abundant free megakaryocyte nuclei in the bone marrow. This is thought to be mediated by antibodies directed against platelets that also destroy the megakaryocytes. Infiltrative or dysplastic bone marrow disorders causing thrombocytopenia are easy to identify on a bone marrow smear.

Because IMT is a diagnosis of exclusion, tick-borne diseases (e.g., canine ehrlichiosis, Rocky Mountain spotted fever, cyclic thrombocytopenia, babesiosis, bartonellosis) should theoretically be ruled out by evaluating the appropriate serology or PCR and a blood smear. However, if the animal does not have clinical signs unrelated to the bleeding, the thrombocytopenia is not likely caused by sepsis or tick-borne diseases, although occasionally asymptomatic thrombocytopenic dogs have subclinical rickettsial diseases. If sepsis is suspected on the basis of clinical signs and clinicopathologic findings (e.g., fever, tachycardia, poor perfusion, degenerative left shift in the leukogram, hypoglycemia, hyperbilirubinemia), urine and blood should be obtained for bacterial cultures.

The presence of spherocytic hemolytic anemia or autoagglutination in a dog with thrombocytopenia is highly suggestive of Evans syndrome (combination of IMT and immune hemolytic anemia [IHA]). A direct Coombs test is usually positive in these cases. On rare occasions a direct Coombs test is positive in a dog with IMT and borderline anemia, further supporting a diagnosis of Evans syndrome.

A hemostasis screen should always be performed to rule out DIC in a thrombocytopenic animal found to have RBC fragments in a blood smear or evidence of secondary bleeding (e.g., hematomas, bleeding into body cavities). The remainder of the hemostasis screen is usually normal in dogs and cats with selective thrombocytopenia.

Several tests are available to evaluate antiplatelet antibodies, including direct immunofluorescence of bone marrow megakaryocytes and enzyme-linked immunosorbent assays for circulating or platelet-bound antibodies (see Chapter 92). However, most of these are not clinically reliable, and a diagnosis of IMT can be made only after other causes of thrombocytopenia have been excluded (i.e., regardless of the results of the antiplatelet antibody tests).

Abdominal radiographs and ultrasonograms may reveal an enlarged spleen not evident during physical examination. Diffuse splenomegaly (i.e., splenic sequestration of platelets) may be the cause of the thrombocytopenia, or it may reflect "work hypertrophy" (i.e., mononuclear phagocytic system hyperplasia) and extramedullary hematopoiesis in a dog with IMT. Splenic nodules are usually an incidental finding in dogs with thrombocytopenia, and they may represent extramedullary hematopoiesis or hyperplasia; fine-needle aspiration of the nodules should establish a cytologic diagnosis. Despite the low platelet counts, clinically relevant bleeding rarely occurs.

Often a specific diagnosis of IMT is obtained only after a therapeutic trial with corticosteroids (see later discussion) results in resolution of the thrombocytopenia. If the clinician is in doubt regarding whether the thrombocytopenia is caused by a rickettsial disease or IMT (in dogs), immunosuppressive doses of corticosteroids can be administered in conjunction with doxycycline (5 to 10 mg/kg PO q12-24h) until serologic or PCR test results become available. This combination of agents has no deleterious effects on dogs with rickettsial diseases.

Blood or blood products should be transfused as needed (see Chapter 83). However, the transfusion of whole fresh blood, platelet-rich plasma, or platelets rarely, if ever, results in normalization of the platelet count or even in increases in the platelet count to "safe" levels.

#### Immune-Mediated Thrombocytopenia

IMT is the most common cause of spontaneous bleeding in dogs but is rare in cats. It affects primarily middle-aged, female dogs, and Cocker Spaniels and Old English Sheep-dogs are overrepresented. The clinical signs are those of a primary hemostatic defect and include petechiae, ecchymoses, and mucosal bleeding. Acute collapse may occur if bleeding is pronounced; if the anemia is mild, most dogs are fairly asymptomatic. IMT is acute or peracute in onset in most dogs. During physical examination, signs of primary

hemostatic bleeding (e.g., petechiae, ecchymoses, mucosal bleeding) with or without splenomegaly may be found.

The complete blood count in dogs with IMT is characterized by thrombocytopenia with or without anemia (depending on the degree of spontaneous bleeding and the presence or absence of concurrent IHA); leukocytosis with a left shift may also be present. As a general rule, hematologic changes are limited to the thrombocytopenia. If IHA is associated with IMT (i.e., Evans syndrome), a Coombs-positive, regenerative anemia with spherocytosis or autoagglutination is usually present. Bone marrow cytologic studies typically reveal megakaryocytic hyperplasia, although megakaryocytic hypoplasia with free megakaryocyte nuclei is occasionally present. In addition to the thrombocytopenia, the bleeding time is the only other abnormal test result (ACT, APTT, OSPT, FDP, and fibrinogen concentration are normal). An inverse linear correlation is usually present between the platelet count and the BMBT (i.e., a longer BMBT with lower platelet counts). Ideally, tick-borne diseases and druginduced thrombocytopenia should be ruled out before establishing a definitive diagnosis of IMT.

If the index of suspicion for IMT is high (i.e., a fairly asymptomatic dog with spontaneous primary hemostatic bleeding and thrombocytopenia as the sole hematologic abnormality), a therapeutic trial with immunosuppressive doses of corticosteroids (equivalent to 2 to 8 mg/kg/day of prednisone) should be instituted. Responses are usually seen within 24 to 96 hours. No clinical evidence exists that dexamethasone is more effective than prednisone in controlling IMT. Indeed, in my experience acute gastrointestinal tract ulceration is considerably more prevalent in dogs receiving dexamethasone than in those receiving prednisone. Because an acute upper gastrointestinal tract bleed is usually catastrophic in a dog with thrombocytopenia, prednisone is my drug of choice. H2-antihistamines, such as famotidine (0.5 mg/kg PO q24h), should be used in combination with the corticosteroids.

Fresh whole blood, stored blood, packed RBCs, or hemoglobin solutions should be administered as needed to maintain adequate oxygen-carrying capacity (see Transfusion Therapy in Chapter 83). In addition to immunosuppressive doses of corticosteroids, cyclophosphamide, given intravenously or orally in a single dose of 200 to 300 mg/m<sup>2</sup>, is effective for inducing remission. However, it should not be used as a maintenance agent because it usually causes sterile hemorrhagic cystitis when used on a long-term basis. Vincristine, at a dose of 0.5 mg/m<sup>2</sup> given intravenously, traditionally has been recommended for dogs with IMT. This drug stimulates megakaryocyte endomitosis, resulting in early platelet release from the bone marrow. However, because vinca alkaloids bind to tubulin, the platelets released prematurely are not fully functional (tubulin is responsible for platelet aggregation), and the patients may have further bleeding before the platelet count increases. As discussed in Chapters 85 and 93, human intravenous immunoglobulin (0.5 to 1 g/kg, single dose) can also be used successfully in dogs with refractory or life-threatening IMT.

Failure to induce remission (i.e., to normalize the platelet count) is usually the result of insufficient drug (low doses or the need for a second agent), insufficient duration of therapy (the drugs have not yet had time to become effective), or an incorrect diagnosis. In the event of one of these, the treatment protocol can easily be amended, with the thrombocytopenia usually resolving as a result. Azathioprine (50 mg/m<sup>2</sup> PO q24-48h) is effective in maintaining remission but is not a good agent for inducing remission. In some dogs azathioprine is better tolerated than long-term corticosteroid therapy, although close hematologic monitoring is recommended given its myelosuppressive properties and potential for hepatotoxicity. The androgenic steroid danazol or cyclosporine A may also be beneficial in dogs with IMT. (See Chapter 93 for additional information and drug dosages.)

The prognosis is good in most dogs with IMT, although they may require lifelong treatment. Dogs with refractory IMT can be successfully treated with vinca-loaded platelets, pulse-dose cyclophosphamide, human immunoglobulin, or splenectomy.

IMT has become more prevalent in cats over the past few years. The typical clinical presentation is different from dogs in that most cats have chronic thrombocytopenia that does not lead to spontaneous bleeding. A platelet count of 10,000 to 30,000/µL is relatively common in an otherwise healthy cat without spontaneous bleeding. I have followed up several of these cats for months to years, and their platelet counts do not increase markedly with treatment. Interestingly, a high proportion of these cats also have regenerative or nonregenerative anemia, neutropenia, lymphocytosis, or combinations thereof. The cytopenias may resolve for no apparent reason, only to have a decrease in another cell line months later. Because most of these cats do not bleed, the clinician should be aware that increasing drug dosages or adding drugs may cause more problems than monitoring the platelet count. My treatment of choice for cats with IMT or immune-mediated cytopenias is a combination of dexamethasone (4 mg q1-2wk) and chlorambucil (20-30 mg/m<sup>2</sup> PO q2wk). I have also successfully used human intravenous immunoglobulin G in a limited number of cats with immune-mediated cytopenias.

#### PLATELET DYSFUNCTION

The presence of primary hemostatic bleeding in a patient with a normal platelet count is highly suggestive of a platelet dysfunction syndrome, although vasculopathies and enhanced fibrinolysis should also be considered. Platelet dysfunction syndromes can be congenital or acquired (Box 87-5); however, they rarely result in spontaneous bleeding. More often a prolonged BMBT is noted preoperatively in an otherwise healthy animal, or the animal has a history of pronounced bleeding during a previous surgery. Congenital platelet dysfunction syndromes are rare, with the notable exception of vWD. Some authors classify vWD among the congenital clotting factor deficiencies; however, because its clinical manifestations are those of a primary hemostatic

mal recessive trait (see later discussion). This disorder has

been reported to occur in more than 50 breeds of dogs but

is more common in Doberman Pinschers, German Shepherd

dogs, Poodles, Golden Retrievers, and Shetland Sheepdogs. In these breeds the defect is inherited as an autosomal dom-

inant trait with incomplete penetrance. In Scottish Terriers and Shetland Sheepdogs, it can be inherited as an autosomal

recessive trait; homozygous dogs have no detectable vWF

concentrations and are usually severely affected. Type 1 vWD

may purportedly occur in association with clinical hypothyroidism in dogs; however, most scientifically controlled

studies have failed to prove an association between vWD and

hypothyroidism. Type 2 vWD was recently reported in dogs

with aortic valvular disease; in those dogs, the high shear

associated with turbulent flow across the valve resulted in

selective depletion of high-molecular-weight VWF multim-

In human beings vWF is produced by megakaryocytes and endothelial cells, circulates in plasma complexed to factor VIII coagulant (factor VIII: C), and is one of the major

adhesive proteins in the body. In the dog, platelets do not contribute as much vWF to plasma as in human beings, vWF

is mainly responsible for causing platelets to adhere to the subendothelial structures (e.g., collagen) in areas of high

shear once endothelial cell damage has occurred, thus initiat-

ing the formation of the primary hemostatic plug (Fig.

87-2). The vWF molecule circulates coiled; it uncoils at the

site of endothelial damage, binds to the subendothelium and

then to the platelet receptors, and the platelets are "reeled"

in to the site of injury. As a consequence, vWD is usually

characterized by primary hemostatic defects (e.g., petechiae,

ecchymoses, mucosal bleeding). However, most dogs with vWD do not bleed spontaneously but rather bleed exces-

sively during or after surgery; excessive bleeding during

teething or estrus can also occur, but petechiae and ecchymoses are rarer. Most dogs with vWD and spontaneous

bleeding seen at our clinic are brought in for evaluation of

diffuse oropharyngeal or vaginal bleeding. People with vWD

can also have low circulating concentrations of factor VIII leading to spontaneous secondary hemostatic bleeding

ers (Tarnow et al., 2005).

defect, I include it in this section. Acquired platelet function disorders are more common; clinically they are mainly secondary to uremia, monoclonal gammopathies, ehrlichiosis, retroviral infections, or drug therapy.

#### von Willebrand Disease

vWD is the most common inherited bleeding disorder in human beings and dogs but is rare in cats. The term *von Willebrand syndrome* is reserved for an acquired vWF deficiency. vWD can be classified into three types (Table 87-4). Dogs with the disease typically have a decreased concentration or activity (type 1 vWD), absence of circulating vWF (type 3 vWD), or low to normal concentrations of an abnormal vWF (type 2 vWD), which result in mild (if any) spontaneous bleeding or, more likely, prolonged surgical bleeding. In dogs vWD can be inherited as an autosomal dominant trait with incomplete penetrance or, more rarely, an autoso-



BOX 87-5

Platelet Function Defects in Dogs and Cats

#### **Hereditary**

vWD (many breeds)

Glanzmann's thromboasthenic thrombopathia (Otterhounds, Great Pyrenees)

Canine thrombopathia (Basset Hounds, Foxhounds)

Collagen-deficiency diseases or Ehlers-Danlos syndrome (many breeds)

Scottsyndrome (lack of platelet procoagulant activity) (German Shepherd dogs)

#### **Acquired**

Drugs (prostaglandin inhibitors, antibiotics, phenothiazines, vaccines)

Secondary to diseases (myeloproliferative disorders, systemic lupus erythematosus, renal disease, liver disease, dysproteinemias)

vWD, von Willebrand disease.



TABLE 87-4

Classification of vWD in Dogs

TYPE	DEFECT	BREEDS
1	Low concentration of normal vWF	Airedale Terrier, Akita, Corgi, Dachshund, Doberman Pinscher, German Shepherd dog, Golden Retriever, Greyhound, Irish Wolfhound, Manchester Terrier, Poodle, Schnauzer, Shetland Sheepdog
2	Low concentration of abnormal vWF Absence of vWF	German Shorthaired Pointer, German Wirehaired Pointer Familial: Chesapeake Bay Retriever, Scottish Terrier, Shetland Sheepdog Sporadic: Border Collie, Bull Terrier, Cocker Spaniel, Labrador Retriever, Pomeranian

Modified from Brooks M: von Willebrand disease. In Feldman BF et al, editors: Schalm's veterinary hematology, ed 5, Philadelphia, 2000, Lippincott Williams & Wilkins, p 509.

vWD, von Willebrand disease; vWF, von Willebrand factor.

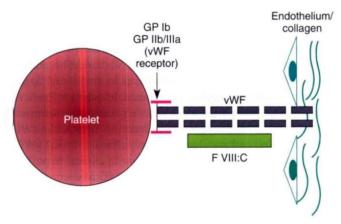


FIG 87-2
The interaction between vWF, platelet, and subendothelial surfaces. GP, Glycoprotein; vWF, von Willebrand factor; FVIII: C, factor VIII coagulant.

(i.e., the clinical findings of hemophilia A); however, this is extremely rare in dogs. Perinatal death or abortions/stillbirths are common in litters with vWD.

The hemostasis screen results are normal in most dogs with vWD. The platelet counts in dogs with vWD are also normal. However, the results of a PFA-100 or BMBT usually inversely correlate with the degree of vWF deficiency (i.e., the PFA-100 closure time or the BMBT is prolonged if the vWF concentration or activity is low). Indeed, the BMBT may be the most cost-effective method for screening dogs for vWD, although its results are not foolproof. It can be done before surgery in breeds at risk or if the owner or breeder is interested in determining whether the dog is likely to have this disorder. However, a normal bleeding time does not necessarily rule out vWD. At our clinic we routinely use the PFA-100 before surgery in dogs at high risk for vWD so that appropriate therapy can be instituted before or during surgery. A diagnosis of vWD can be confirmed by quantifying vWF in specialized veterinary coagulation laboratories. Genetic testing for vWD in specific breeds is available through commercial diagnostic laboratories.

Most dogs with type 1 vWD can be successfully treated before surgery or during a bleeding episode with desmopressin acetate (DDAVP), which causes a massive release of vWF from the endothelial cells and results in shortening of the BMBT and the PFA-100 closure times within 30 minutes of administration. A single 1 µg/kg dose of DDAVP (intranasal preparation) given subcutaneously consistently lessens bleeding in dogs with type 1 vWD despite modest increases in vWF concentration. DDAVP is not effective in dogs with types 2 or 3 vWD because these dogs either lack or have an abnormal (i.e., nonfunctional) vWF. Cryoprecipitate is the blood component of choice for dogs with vWD; a unit of cryoprecipitate is defined as the volume obtained from a unit of fresh frozen plasma. We dose it at 1 U cryoprecipitate per 10 kg of body weight; therefore, a Doberman Pinscher typically receives 3 U. If cryoprecipitate is not available, fresh frozen plasma or whole fresh blood can be used. DDAVP can

also be administered to the blood donor dog 1 hour before blood is collected to maximize the yield of vWF. The use of topical hemostatic agents such as fibrin, collagen, or methacrylate is also indicated to control the local bleeding. As is the case in dogs with other inheritable disorders, dogs with congenital vWD should not be bred.

#### **Other Congenital Platelet Function Defects**

Platelet function defects leading to spontaneous primary hemostatic bleeding have been reported in at least three breeds of dogs (Otterhounds, Foxhounds, and Basset Hounds). The clinical signs and clinicopathologic abnormalities are similar to those seen in dogs with vWD, but the vWF concentrations are normal or high. A syndrome of spontaneous and postoperative bleeding resembling Scott syndrome in human beings from a lack of platelet procoagulant activity was described in German Shepherd dogs (Brooks et al., 2002).

#### SECONDARY HEMOSTATIC DEFECTS

Dogs with secondary hemostatic defects are usually evaluated because of collapse, exercise intolerance, dyspnea, abdominal distention, lameness, or masses. The collapse and exercise intolerance are usually caused by anemia resulting from intracavitary bleeding, as is the dyspnea and abdominal distention. The lameness is usually caused by hemarthrosis, and the masses or lumps usually represent hematomas. Cats and dogs with secondary hemostatic disorders do not have petechiae or ecchymoses, and mucosal bleeding (e.g., melena, epistaxis) is rarely seen. In general the severity of the bleeding is directly related to the severity of the deficiency of the clotting factor(s). Liver disease and rodenticide poisoning leading to vitamin K deficiency are the two most common causes of secondary hemostatic defects seen at our clinic. As previously noted, these disorders are more common in dogs than in cats.

### CONGENITAL CLOTTING FACTOR DEFICIENCIES

Congenital clotting factor deficiencies, as well as the breeds affected, are listed in Box 87-3. They are relatively common in dogs but are rare in cats. Most genetic mutations leading to these defects have been well characterized, and some laboratories now offer genetic testing for congenital coagulopathies. Hemophilia A and B are sex-linked traits; the modes of inheritance of other coagulopathies vary. In affected animals the severity of the bleeding is usually inversely proportional to the concentration of the individual clotting factor affected (e.g., bleeding is more severe in association with a very low factor activity). Clinical signs usually include spontaneous hematoma formation, which the owners may describe as "lumps," and bleeding into body cavities as well as signs compatible with "fading puppy syndrome" and protracted umbilical cord bleeding after birth. Abortions or stillbirths in the litter are common. Petechiae and ecchymoses are not present in dogs with congenital clotting factor deficiencies. Cats with congenital clotting factor deficiency usually do not bleed spontaneously, but rather have intraoperative or delayed postoperative bleeding.

Carriers of the defect may be asymptomatic but usually have prolonged clotting times in vitro. Certain factor deficiencies (so-called "contact factors"), including factors XII and XI, Fletcher factor (prekallikrein), and HMWK, are also found in otherwise asymptomatic animals (i.e., no excessive  $bleeding) with {\it markedly prolonged APTTs}. However, massive$ and often life-threatening postoperative bleeding starting 24 to 36 hours after surgery is common in dogs with factor XI deficiency.

Most dogs and cats with congenital coagulopathies are treated with supportive and transfusion therapies; no other treatments appear to be beneficial. As with animals with other congenital defects, dogs and cats with coagulopathies should not be bred.

#### VITAMIN K DEFICIENCY

Vitamin K deficiency in small animals usually results from the ingestion of vitamin K antagonists (warfarin, diphacinone, or their derivatives, brodifacoum and bromadiolone), although it can also occur as a consequence of malabsorption in dogs and cats with obstructive cholestasis, infiltrative bowel disease, or liver disease. Four clotting factors are vitamin K dependent: factors II, VII, IX, and X. Proteins C and S, two natural anticoagulants, are also vitamin K dependent. Because of its clinical relevance, the following discussion focuses only on rodenticide poisoning, which is more common in dogs and extremely rare in cats.

Most dogs with toxicity are evaluated because of acute collapse and a possible history of rodenticide ingestion. Coughing, thoracic pain, and dyspnea are also common. These dogs usually have clinical signs compatible with secondary bleeding, such as hematomas and bleeding into body cavities. The most common site of bleeding in dogs evaluated at our clinic is the thorax; some dogs have superficial skin bruising in areas of friction, such as the axilla or the groin. Other abnormalities include pale mucous membranes, anemia (usually regenerative if sufficient time has elapsed since the acute bleeding episode), and hypoproteinemia. Sudden death may occur as a result of central nervous system or pericardial hemorrhage.

If the rodenticide has been ingested minutes to hours before presentation, induced vomiting and the administration of activated charcoal may eliminate or neutralize most of it. If the ingestion is questionable and no clinical signs of coagulopathy are present (e.g., hemothorax, hemoabdomen, bruising), determination of the OSPT is recommended. Because factor VII is the shortest lived vitamin K-dependent protein (circulating half-life of 4 to 6 hours), the OSPT is usually prolonged before spontaneous bleeding becomes evident. Newer tests for proteins induced by vitamin K absence may also aid in the early diagnosis of rodenticide toxicity, but they are not used in our clinic because they seem to lack clinical relevance.

The typical hemostasis screen in a dog with symptomatic vitamin K deficiency reveals marked prolongation of the OSPT and APTT; this is one of the few clinical situations where the OSPT is typically longer than the APTT. The FDP test is positive in more than half of affected dogs and mild thrombocytopenia is present (70,000 to 125,000/μL), which is likely caused by an excessive consumption of platelets from protracted bleeding.

These animals usually require immediate transfusions of whole fresh blood or fresh frozen plasma (or cryo-poor plasma) to replenish the coagulation factors (and packed RBCs if the animal is anemic). From 8 to 12 hours may elapse before vitamin K therapy appreciably shortens the OSPT and subsequently decreases bleeding.

Vitamin K is available in several forms, but vitamin  $K_1$  is the most effective. It is available for oral or parenteral use. Intravenous administration of vitamin K is not recommended because of the risk of anaphylactic reactions or Heinz body formation; intramuscular injections in a dog with a coagulopathy usually result in hematoma formation. Subcutaneous administration of vitamin K<sub>1</sub> with a 25-gauge needle (loading dose of 5 mg/kg, followed in 8 hours by 2.5 mg/kg SQ divided q8h) is preferred if the patient is properly hydrated. Administration of oral loading doses of vitamin K1 has been advocated for the treatment of dogs with rodenticide poisoning (5 mg/kg with a fatty meal, then 2.5 mg/kg divided q8-12h); this is the treatment used in our clinic. Because vitamin K is lipid soluble, its absorption is enhanced if it is given with fatty meals. Animals with cholestatic or malabsorptive syndromes may require continued subcutaneous injections of vitamin K. In critical cases the OSPT should be monitored every 8 hours until it normalizes.

If the anticoagulant is known to be warfarin or another first-generation hydroxycoumarin, 1 week of oral vitamin K<sub>1</sub> is usually sufficient to reverse the coagulopathy. However, if it is indanedione or any of the second- or third-generation anticoagulants, oral vitamin K1 therapy must be maintained for at least 3 weeks and possibly as long as 6 weeks. Most currently available rodenticides contain second- and thirdgeneration anticoagulants. If the rodenticide ingested is unknown, the animal should be treated for 1 week, at which time vitamin K treatment is discontinued. An OSPT is then determined within 24 to 48 hours of the last dose. If the OSPT is prolonged, therapy should be reinstituted and maintained for 2 more weeks and the OSPT reevaluated at the end of this period.

#### MIXED (COMBINED) HEMOSTATIC DEFECTS

#### DISSEMINATED INTRAVASCULAR COAGULATION

DIC, previously called consumptive coagulopathy or defibrination syndrome, is a complex syndrome in which excessive intravascular coagulation leads to multiple-organ microthrombosis (multiple organ failure [MOF]) and paradoxic bleeding caused by the inactivation or excessive consumption of platelets and clotting factors as a result of enhanced fibrinolysis. DIC is not a specific disorder but rather a common pathway in a variety of disorders. Moreover, DIC constitutes a dynamic phenomenon in which the patient's status and the results of coagulation tests change markedly, rapidly, and repeatedly during treatment. This syndrome is relatively common in dogs and cats.

#### **Pathogenesis**

Several general mechanisms can lead to activation of intravascular coagulation and therefore to the development of DIC, including the following:

- · Endothelial damage
- Platelet activation
- · Release of tissue "procoagulants"

Endothelial damage commonly results from electrocution or heat stroke, although it may also play a role in sepsis-associated DIC. Platelets can be activated by a variety of stimuli, but mainly they are activated by viral infections (e.g., FIP in cats) or sepsis. Tissue procoagulants (likely tissue factor) are released in several common clinical conditions, including trauma, hemolysis, pancreatitis, bacterial infections, acute hepatitis, and possibly some neoplasms (e.g., HSA).

The best way to understand the pathophysiologic process of DIC is to think of the entire vascular system as a single, giant blood vessel and the pathogenesis of the disorder as an exaggeration of the normal hemostatic mechanisms. Once the coagulation cascade has been activated in this "giant vessel" (i.e., it is widespread within the microvasculature in the body), several events take place. Although they are described sequentially, most of them actually occur simultaneously, and the intensity of each varies with time, thus making for an extremely dynamic process.

First, the primary and secondary hemostatic plugs are formed (see p. 1242). Because this is happening in thousands or tens of thousands of small vessels simultaneously, multiple thrombi form in the microcirculation. If this process is left unchecked, ischemia (resulting in MOF) eventually develops. During this excessive intravascular coagulation, platelets are consumed and destroyed in large quantities, leading to thrombocytopenia. Second, the fibrinolytic system is activated systemically, resulting in clot lysis and the inactivation (or lysis) of clotting factors and impaired platelet function. Third, AT and possibly proteins C and S are consumed in an attempt to halt intravascular coagulation, leading to "exhaustion" of the natural anticoagulants. Fourth, the formation of fibrin within the microcirculation leads to the development of hemolytic anemia and further compounds the thrombocytopenia as the RBCs are sheared by these fibrin strands (i.e., fragmented RBCs or schistocytes).

When all these events are considered, it is easy to understand (1) why an animal with multiple organ thrombosis

(caused by excessive intravascular coagulation and the depletion of natural anticoagulants) is bleeding spontaneously (as a result of thrombocytopenia, impaired platelet function, and inactivation of clotting factors) and (2) why one of the therapeutic approaches that appears to be beneficial in halting the bleeding in dogs and cats with DIC is to paradoxically administer heparin or other anticoagulants (i.e., if sufficient AT is available, heparin halts intravascular coagulation, which in turn decreases activation of the fibrinolytic system, thus releasing its inhibitory effect on the clotting factors and platelet function).

In addition to the events just described, impaired tissue perfusion results in the development of secondary "enhancers" of DIC, including hypoxia; acidosis; and hepatic, renal, and pulmonary dysfunction; and the release of myocardial depressant factor. The function of the mononuclear-phagocytic system also is impaired so that FDPs and other byproducts, as well as bacteria absorbed from the intestine, cannot be cleared from the circulation. These factors also must be dealt with therapeutically (see p. 1256).

The prevalence of primary disorders associated with DIC in 50 dogs and 21 cats recently evaluated at The Ohio State University Veterinary Teaching Hospital (OSU-VTH) is depicted in Table 87-5. Neoplasia (primarily HSA), liver disease, and immune-mediated blood diseases were the most common disorders associated with DIC in dogs; liver disease (primarily hepatic lipidosis), neoplasia (mainly lymphoma), and FIP were the disorders most frequently associated with DIC in cats.

At our clinic, symptomatic DIC in dogs (i.e., that associated with bleeding) is most commonly associated with HSA, followed by sepsis, pancreatitis, hemolytic anemia, gastric dilation-volvulus, and liver disease. Symptomatic DIC is extremely rare in cats but hemostatic evidence of DIC is common, accounting for approximately two thirds of the abnormal hemostatic profiles in this species in our clinic. As previously discussed, DIC is common in cats with liver disease, malignant neoplasms, or FIP. We have also observed symptomatic DIC in two cats receiving methimazole. The pathogenesis of DIC in dogs with HSA appears to be complex and multifactorial; the major mechanism triggering intravascular coagulation in dogs with this neoplasm was believed to be the abnormal irregular endothelium in the neoplasm (i.e., exposure to subendothelial collagen and the activation of coagulation). However, some canine HSAs appear to synthesize a cancer procoagulant because dogs with small HSAs can have severe DIC, whereas some dogs with widely disseminated HSA have normal hemostasis.

#### **Clinical Features**

Dogs with DIC can have several clinical presentations; the two common forms are chronic silent (subclinical) and acute (fulminant) DIC. In the chronic silent form, the patient does not have evidence of spontaneous bleeding, but clinicopathologic evaluation of the hemostatic system reveals abnormalities compatible with this syndrome (see the next page). This form of DIC appears to be common in dogs with



TABLE 87-5

Primary Disorders Associated with DIC in 50 Dogs and 21 Cats Evaluated at The OSU-VTH

DISEASE	DOGS (%)	CATS (%)
Neoplasia	18	29
HSA	8	5
Carcinoma	4	10
LSA	4	14
HA	2	0
Liver disease	14	33
Cholangiohepatitis	4	0
Lipidosis	0	24
PSS	4	0
Cirrhosis	2	0
Unspecified	4	10
Pancreatitis	4	0
Immune-mediated diseases	10	0
IHA	4	0
IMT	2	0
Evans syndrome	2 2 2	0
IMN	2	0
Infectious diseases	10	19
FIP	0	19
Sepsis	8	0
Babesiosis	2	2
Rodenticide*	8	0
GDV	6	0
HBC	4	0
Miscellaneous	18	19

Reprinted from Couto CG: Disseminated intravascular coagulation in dogs and cats, *Vet Med* 94:547, 1999. This table originally appeared in the June 1999 issue of *Veterinary Medicine*. It is reprinted here by permission of Thomson Veterinary Healthcare Communications, 8033 Flint, Lenexa, KS 66214; [913] 492-4300; fax: [913] 492-4157; www.vetmedpub.com. All rights reserved. \* The results of hemostasis profiles in dogs with rodenticide toxicity mimic those seen in DIC.

DIC, Disseminated intravascular coagulation; OSU-VTH, Ohio State University Veterinary Teaching Hospital; HSA, hemangiosarcoma; LSA, lymphoma; HA, hemangioma; PSS, portosystemic shunt; IHA, immune-mediated hemolytic anemia; IMT, immune-mediated thrombocytopenia; IMN, immune-mediated neutropenia; FIP, feline infectious peritonitis; GDV, gastric dilation-volvulus; HBC, hit by car.

malignancy and other chronic disorders. The acute form may represent a true acute phenomenon (e.g., after heatstroke, electrocution, or acute pancreatitis) or, more commonly, it represents acute decompensation of a chronic, silent process (e.g., HSA). Acute DIC is extremely rare in cats. Regardless of the pathogenesis, dogs with acute DIC often are brought in because of profuse spontaneous bleeding and constitutional signs attributable to anemia or parenchymal organ thrombosis (i.e., MOF). The clinical signs of bleeding indicate both primary bleeding (e.g., petechiae, ecchymoses, mucosal bleeding) and secondary bleeding (blood in body cavities). Clinical and clinicopathologic evidence of organ

dysfunction is also present. Most cats with DIC seen at our clinic do not have evidence of spontaneous bleeding; clinical signs in these cats are those associated with the primary disease.

In a recent retrospective study of 50 dogs with DIC conducted in our clinic, only 26% had evidence of spontaneous bleeding, whereas only one of 21 cats with DIC had evidence of spontaneous bleeding. Most patients were presented for evaluation of their primary problem and were not bleeding spontaneously; DIC was diagnosed as part of the routine clinical evaluation.

#### **Diagnosis**

Because clinical DIC is uncommon in cats, the discussion on diagnosis and treatment focuses on dogs. Several hematologic findings help support a presumptive clinical diagnosis of DIC and include a regenerative hemolytic anemia (although occasionally, because the animal has a chronic disorder such as cancer, the anemia is nonregenerative), hemoglobinemia (caused by intravascular hemolysis), RBC fragments or schistocytes, thrombocytopenia, neutrophilia with a left shift, and rarely neutropenia. Most of these features are evident with evaluation of a spun hematocrit and a blood smear.

Serum biochemical abnormalities in dogs with DIC include hyperbilirubinemia from hemolysis or hepatic thrombosis, azotemia and hyperphosphatemia if severe renal microembolization has occurred, an increase in liver enzyme activities caused by hypoxia or hepatic microembolization, a decreased total carbon dioxide content caused by metabolic acidosis, and panhypoproteinemia if the bleeding is severe enough. Another manifestation of MOF is the development of multifocal ventricular premature contractions detected in an electrocardiogram.

Urinalysis usually reveals hemoglobinuria and bilirubinuria and occasionally proteinuria and cylindruria. Urine samples in dogs with acute DIC should not be obtained by cystocentesis because severe intravesical or intramural bleeding may result.

Hemostatic abnormalities in dogs with DIC include thrombocytopenia, a prolongation of the OSPT or APTT (more than 25% of the concurrent control), normal or low fibrinogen concentration, a positive FDP or D-dimer test, and a decreased AT concentration. Using a TEG, fibrinolysis can be enhanced in these animals. At our clinic, DIC is diagnosed if the patient has four or more of the hemostatic abnormalities just described, particularly if schistocytes are present.

The hemostatic abnormalities in 50 dogs and 21 cats with DIC evaluated in our clinic are listed in Table 87-6. In dogs thrombocytopenia, prolongation of the APTT, anemia, and schistocytosis were common; in contrast with previous descriptions of the syndrome in dogs, regenerative anemia, prolongation of the OSPT, and hypofibrinogenemia were not. In cats prolongation of the APTT and/or OSPT, schistocytosis, and thrombocytopenia were common, whereas the presence of FDPs and hypofibrinogenemia were rare.



TABLE 87-6

Hemostatic Abnormalities in 50 Dogs and 21 Cats with DIC Evaluated at The OSU-VTH

DOGS (%)	CATS (%)
90	57
88	100
76	67
64	24
42	<i>7</i> 1
14	5
	90 88 76 64 42

From Couto CG: Disseminated intravascular coagulation in dogs and cats, *Vet Med* 94:547, 1999.

DIC, Disseminated intravascular coagulation; OSU-VTH, Ohio State University Veterinary Teaching Hospital; APTT, activated partial thromboplastin time; FDPs, fibrin degradation products; OSPT, one-stage prothrombin time.



BOX 87-6

Treatment of Dogs and Cats with DIC

- 1. Eliminate the precipitating cause
- 2. Halt intravascular coagulation:

Heparin

Mini dose: 5-10 IU/kg SQ q8h

- Low dose: 50-100 IU/kg SQ q8h
- Intermediate dose: 300-500 IU/kg SQ or IV q8h
- High dose: 750-1000 IU/kg SQ or IV q8h
   Blood or blood products (provide AT, other anticoagulants, and clotting factors)
- 3. Maintain parenchymal organ perfusion:

Aggressive fluid therapy

4. Prevent secondary complications:

Oxygen

Correct acid-base imbalance

Antiarrhythmics

**Antibiotics** 

DIC, Disseminated intravascular coagulation; AT, antithrombin.

#### **Treatment**

Once a diagnosis of DIC has been established (or even if the degree of suspicion is high that DIC is present), treatment should be instituted without delay. Unfortunately, no controlled clinical trials have been performed in veterinary medicine evaluating the effects of different treatments in dogs with DIC. Therefore the following discussion reflects my beliefs in the management of dogs with this disorder (Box 87-6).

Unquestionably, removing or eliminating the precipitating cause constitutes the main therapeutic goal in patients with DIC. However, this is not always possible. Conditions in which the precipitating causes can be eliminated include a primary HSA (surgical excision), disseminated or meta-

static HSA (chemotherapy), sepsis (appropriate antimicrobial treatment), and IHA (immunosuppressive treatment). In most other situations (e.g., electrocution, heatstroke, pancreatitis) the cause can rarely be eliminated within a short time. Therefore the treatment of dogs with DIC is aimed at the following:

- Halting intravascular coagulation
- · Maintaining good parenchymal organ perfusion
- · Preventing secondary complications

Of note, if blood and blood products were available in an unlimited supply (such as is the case in most human hospitals), dogs with DIC would not die of hypovolemic shock. Most dogs with DIC die of pulmonary or renal dysfunction. At our clinic, "DIC lungs" (i.e., intrapulmonary hemorrhages with alveolar septal microthrombi) appear to be a common cause of death in these patients.

Halting intravascular coagulation. I use a dual approach to halt intravascular coagulation: the administration of heparin and blood or blood products. As previously mentioned, heparin is a cofactor for AT and therefore is not effective in preventing the activation of coagulation unless AT activity in the plasma is sufficient. Because AT activity in animals with DIC is usually low as a result of consumption and possibly inactivation, the patient should be provided with sufficient quantities of this anticoagulant. The most cost-efficient way of achieving this is to administer fresh frozen plasma. The old adage that administering blood or blood products to a dog with DIC is analogous to "adding logs to a fire" has not been true in my experience. Therefore blood or blood products should never be withheld based solely on this belief.

Heparin has been used historically to treat DIC in human beings and dogs. However, controversy still exists regarding whether it is beneficial. At our clinic the survival rate in dogs with DIC has increased markedly since we routinely started using heparin and blood products. Although this can also be attributed to improvement in patient care, I believe that heparin is beneficial in such patients and indeed may be responsible for the increased survival rate.

Sodium heparin is given in a wide range of doses. Following are the four traditional dose ranges:

- · Mini dose: 5 to 10 IU/kg SQ q8h
- Low dose: 50 to 100 IU/kg SQ q8h
- Intermediate dose: 300 to 500 IU/kg SQ or IV q8h
- · High dose: 750 to 1000 IU/kg SQ or IV q8h

I routinely use low-dose heparin in combination with the transfusion of blood or blood components. The rationale for this is that this dose of heparin does not prolong the ACT or APTT in normal dogs (a minimum of 150 to 250 IU/kg q8h is required to prolong the APTT in normal dogs), and it appears to be biologically active in these animals given that some of the clinical signs and hemostatic abnormalities are reversed in animals receiving this dosage. The fact that it

does not prolong the APTT or ACT is extremely helpful in dogs with DIC. For example, if a dog with DIC is receiving intermediate-dose heparin, it is then impossible to predict, on the basis of hemostatic parameters, whether a prolongation of the APTT is caused by excessive heparin administration or progression of this syndrome. As laboratory heparin determinations become widely available, this may become a moot point. Until then, my clinical impression is that if an animal with DIC receiving mini- or low-dose heparin shows a prolonged ACT or APTT, the intravascular coagulation is deteriorating and a treatment change is necessary. The use of low-molecular-weight heparin in dogs with DIC is currently being investigated. In an experimental model of DIC in Beagles, high doses of low-molecular-weight heparin resulted in resolution of the clinicopathologic abnormalities associated with DIC (Mischke et al., 2005).

Lepirudin, a novel leech recombinant AT, recently proved beneficial in preventing MOF in an experimental model of sepsis with enteric organisms in Greyhounds. However, this treatment is currently cost prohibitive.

If evidence of severe microthrombosis is present (e.g., marked azotemia, increase in liver enzyme activity, ventricular premature contractions), dyspnea, or hypoxemia, intermediate- or high-dose heparin can be used, with the goal of prolonging the ACT to 2 to 2.5 times the baseline value, or normal if the baseline time was already prolonged. If overheparinization occurs, protamine sulfate can be administered by slow intravenous infusion (1 mg for each 100 IU of the last dose of heparin; 50% of the calculated dose is given I hour after the heparin and 25% 2 hours after the heparin). The remainder of the dose can be administered if clinically indicated. Protamine sulfate should be administered with caution because it can be associated with acute anaphylaxis in dogs. Once improvement in the clinical and clinicopathologic parameters has been achieved, the heparin dose should be tapered gradually (over 1 to 3 days) to prevent rebound hypercoagulability, a phenomenon commonly observed in human beings.

Aspirin and other antiplatelet agents can also be given to prevent platelet activation and thus halt intravascular coagulation. Doses of 0.5 to 10 mg/kg of aspirin given orally every 12 hours in dogs and every third day in cats have been recommended, although in my experience aspirin is rarely of clinical benefit. If it is used, the patient should be closely watched for severe gastrointestinal tract bleeding, because this NSAID can cause gastroduodenal ulceration, which could be catastrophic in a dog with a severe coagulopathy such as DIC.

#### Maintaining good parenchymal organ perfusion.

Good parenchymal organ perfusion is best achieved with aggressive fluid therapy consisting of crystalloids or plasma expanders such as dextran (see Table 87-6). The purpose of this therapy is to dilute out the clotting and fibrinolytic factors in the circulation, flush out microthrombi from the microcirculation, and maintain the precapillary arterioles patent so that blood is shunted to areas in which oxygen exchange is efficient. However, care should be taken not to

overhydrate an animal with compromised renal or pulmonary function.

Preventing secondary complications. As previously discussed, numerous complications occur in dogs with DIC. Attention should be directed toward maintaining oxygenation (by oxygen mask, cage, or nasopharyngeal catheter), correcting acidosis, eliminating cardiac arrhythmias, and preventing secondary bacterial infections (i.e., the ischemic gastrointestinal mucosa no longer functions as an effective barrier to microorganisms, bacteria are absorbed and cannot be cleared by the hepatic mononuclear-phagocytic system, and sepsis occurs).

Prognosis. The prognosis for dogs with DIC is still grave. Despite the numerous acronyms for DIC coined over the past few decades (e.g., "death is coming," "dead in cage," "dog in cooler"), if the inciting cause can be controlled most patients recover with appropriate treatment (see Fig. 87-2). In the retrospective study of DIC in dogs conducted at OSU-VTH the mortality rate was 54%; however, the mortality rate in dogs with minor changes in the hemostasis screen (i.e., fewer than three abnormalities) was 37%, whereas that in the dogs with severe hemostatic abnormalities (i.e., more than three hemostatic abnormalities) was 74%. In addition, marked prolongation of the APTT and marked thrombocytopenia were negative prognostic factors. The median APTT in dogs that survived was 46% over the controls, whereas it was 93% over the controls in dogs that did not survive. Likewise, the median platelet count in dogs that survived was 110,000/µL, and in dogs that did not survive it was 52,000/μL.

#### **THROMBOSIS**

Thrombotic and thromboembolic disorders appear to be considerably less common in cats and dogs than in human beings. Several situations can result in thrombosis or thromboembolism (TE), including stasis of blood, activation of intravascular coagulation in an area of abnormal or damaged endothelium, decreased activity of natural anticoagulants, and decreased or impaired fibrinolysis. Thrombosis has been recognized clinically as associated with cardiomyopathy, hyperadrenocorticism, protein-losing enteropathy and nephropathy, and IHA.

Diagnosing TE is not an easy task. Clinical signs are variable and include signs associated with parenchymal organ ischemia (e.g., dyspnea from pulmonary TE, high liver enzyme activities in patients with hepatic TE, intermittent rear limb claudication in dogs with aortic thrombosis). A positive D-dimer test has been reported to be associated with TE disease in dogs (Nelson & Andreasen, 2003). In our experience TEG is a rapid and sensitive test to diagnose TE disease in dogs (Fig. 87-3).

Stasis of blood and possibly an irregular endothelial surface appear to be the major causes in cats with aortic (iliac) TE secondary to hypertrophic cardiomyopathy. Decreased activity of the natural anticoagulant AT plays a major role in the thrombosis seen in dogs with

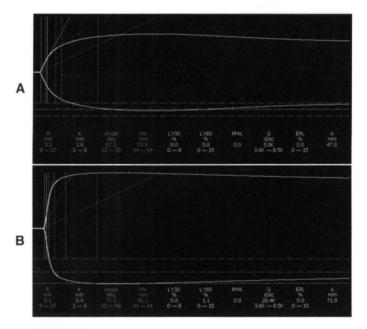


FIG 87-3

**A,** TEG (Haemoscope, Niles, Ill.) tracing in a normal dog; the MA (maximum amplitude) provides information on the strength of the clot and is within the reference range (53.9 mm). **B,** TEG tracing in a dog with hypercoagulability; notice that the MA is 80.3 mm.

protein-losing nephropathy or protein-losing enteropathy; in addition, human beings with hypertension frequently have high concentration of PAI-1, which in turns inhibits fibrinolysis, thus resulting in a net procoagulant effect. This mechanism may also be important in dogs with proteinlosing nephropathy and hypertension. The decreased AT activity stems from the fact that this is a relatively small molecule (approximately 60 kD) that is easily lost in the urine or gut contents in dogs with either of these two disorders. The thrombosis commonly seen in dogs with hyperadrenocorticism is likely related to the induction of PAI-1 synthesis by corticosteroids (corticosteroids inhibit fibrinolysis). An increased risk for TE has been recognized in dogs with IHA. Although the pathogenesis of these disorders is obscure, the release of procoagulants from the lysed RBCs has been postulated as a cause; sludging of autoagglutinated RBCs in the microcirculation is also likely to contribute to this procoagulant state.

Dogs and cats at high risk for thrombosis or TE should receive anticoagulants. The two drugs commonly used in cats and dogs at risk for this condition are aspirin and heparin. Coumarin derivatives are commonly used in human beings, but in dogs and cats they can result in excessive bleeding. In recent reports of human beings with AT deficiency, anabolic steroids such as stanozolol have been suggested to also decrease the risk of thrombotic disorders as a result of their stimulatory effect on the fibrinolytic system. The recognition and management of pulmonary TE are discussed in Chapter 22.

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# CHAPTER Lymphadenopathy and Splenomegaly

#### CHAPTER OUTLINE

APPLIED ANATOMY AND HISTOLOGY
FUNCTION
LYMPHADENOPATHY
SPLENOMEGALY
APPROACH TO PATIENTS WITH
LYMPHADENOPATHY OR SPLENOMEGALY
MANAGEMENT OF PATIENTS WITH
LYMPHADENOPATHY OR SPLENOMEGALY

#### APPLIED ANATOMY AND HISTOLOGY

The lymph nodes and spleen constitute the main source of immunologic and mononuclear-phagocytic (MP) cells in the body. Because these lymphoid structures are in a constant dynamic state, they continuously reshape and change in size in response to antigenic stimuli. In general, the response of the cells within a lymph node to different stimuli is similar to that occurring in the spleen. However, the spleen responds primarily to blood-borne antigens (mainly nonopsonized organisms), whereas the lymph nodes respond to antigens arriving through the afferent lymphatics (i.e., local tissue response). The response of the lymph nodes and spleen to different stimuli is briefly reviewed in this chapter.

The canine and feline lymph nodes are reniform, encapsulated, well-developed structures responsible for filtering lymph and participating in immunologic reactions. Fig. 88-1 depicts the basic microscopic anatomy of a lymph node in a carnivore. It is composed of a capsule, subcapsular spaces, cortex, paracortex, and medulla. Each of these areas has specific functions. The capsule surrounds and supports all other structures within the node (stroma). The subcapsular spaces (or sinuses) contain mainly MP cells responsible for "filtering" particles arriving through the afferent lymphatics and presenting the antigens to the lymphoid cells. The cortex contains mainly B-cell areas in the germinal centers. The paracortex is composed primarily of T cells and is therefore involved in cell-mediated immunity. The medulla

contains the medullary cords, where the committed B cells persist and may expand to solid areas of plasma cells in response to antigenic stimulation. Between the medullary cords, the medullary sinuses form an endothelial sieve containing varying numbers of MP cells, which "screen" the efferent lymph. The lymph flows from the medulla to the efferent lymphatics in the hilus.

An understanding of the different histologic and functional characteristics of these anatomic areas aids in understanding the pathogenesis of lymphadenopathy. For example, a lymph node reacting to a bacterial infection has primarily B-cell hyperplasia characterized by increased numbers of secondary follicles. This histologic/functional compartmentalization should be kept in mind when interpreting cytologic or histopathologic lymph node specimens.

#### **FUNCTION**

The two main functions of the lymph nodes are to filter particulate material and participate in immunologic processes. Particulate material is filtered as lymph flows through the areas rich in MP cells while it moves from the afferent to the efferent lymphatics. During this transit, particulate material is taken up and processed by the MP or antigen processing (AP) cells and presented to the lymphoid cells to generate a humoral or cellular immune response.

The spleen has multiple functions, including hematopoiesis, filtration and phagocytosis, remodeling of red blood cells (RBCs), removal of intraerythrocytic inclusions, storage of RBCs and platelets, metabolizing of iron, and immunologic functions. Because of its nonsinusal nature, the feline spleen is less efficient at removing intracellular inclusions than its canine counterpart.

#### LYMPHADENOPATHY

#### **Etiology and Pathogenesis**

In this chapter lymphadenopathy is defined as lymph node enlargement. According to the distribution, the following

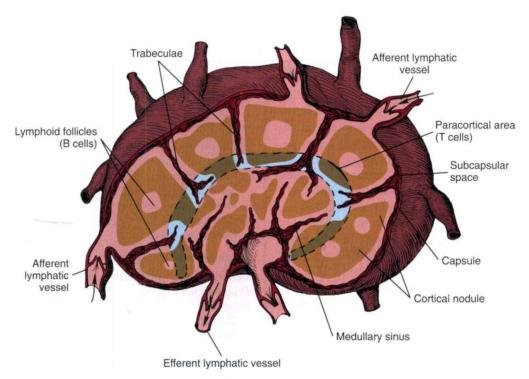


FIG 88-1
Microscopic anatomy of a typical lymph node in a carnivore. (Reprinted from Couto CG: Diseases of the lymph nodes and spleen. In Ettinger SJ, editor: Textbook of veterinary internal medicine—diseases of the dog and cat, ed 3, Philadelphia, 1989, WB Saunders.

terms are used to characterize lymphadenopathy. Solitary lymphadenopathy refers to the enlargement of a single lymph node. Regional lymphadenopathy is an enlargement of a chain of lymph nodes draining a specific anatomic area. Generalized lymphadenopathy is a multicentric lymph node enlargement affecting more than one anatomic area. Lymphadenopathies can also be classified as superficial or deep (or visceral) according to their anatomic location.

Lymph nodes enlarge as a consequence of the proliferation of normal cells that normally reside in the node, or infiltration with normal or abnormal cells. Rarely, lymph nodes enlarge as a result of vascular changes (e.g., hyperemia, congestion, neovascularization, edema).

When normal cells proliferate within a lymph node in response to antigenic stimuli (e.g., vaccination, infection), the term reactive lymphadenopathy (or lymph node hyperplasia) is used. Lymphoid and MP/AP cells proliferate in response to immunologic and infectious stimuli, although occasionally a clinician evaluates a dog or cat in which a cause for the reactive lymphadenopathy cannot be identified. Because these lymphoid structures are usually presented with many antigens simultaneously, the cell proliferation that occurs in reactive lymphadenopathies is polyclonal (i.e., a wide variety of morphologic types of lymphoid and MP/AP cell types are present in a cytologic or histopathologic specimen).

When polymorphonuclear leukocytes or macrophages predominate in the cellular infiltrate, the term *lymphadenitis* 

is used. This is usually, but not always, a result of infectious processes. Depending on the predominant cell type in the infiltrate, lymphadenitides are classified as *suppurative* (neutrophils predominate), *granulomatous* (macrophages predominate), *pyogranulomatous* (macrophages and neutrophils predominate), or *eosinophilic* (eosinophils predominate). A focal area of suppurative inflammation with marked liquefaction (i.e., pus) is referred to as a *lymph node abscess*. The etiologic agents that commonly cause the different types of lymphadenitis are listed in Table 88-1.

Infiltrative lymphadenopathies usually result from the displacement of normal lymph node structures by neoplastic cells and, more rarely, from extramedullary hematopoiesis. Neoplasms affecting the lymph nodes can be either *primary* hematopoietic tumors or *secondary* (metastatic) neoplasms. Lymph node infiltration by hematopoietic malignancies (i.e., lymphoma) constitutes one of the most common causes of generalized lymphadenopathy in dogs.

#### **Clinical Features**

From the clinical standpoint, familiarization with the location and palpation characteristics of normal lymph nodes, which should always be evaluated during a routine physical examination, is important. The following lymph nodes are palpable in normal dogs and cats: the mandibular, prescapular (or superficial cervical), axillary (in approximately half of animals), superficial inguinal, and popliteal (Fig. 88-2). Lymph nodes that are palpable only when markedly enlarged



**TABLE 88-1** 

Classification of Lymphadenopathies in Dogs and Cats

ТҮРЕ	SPECIES	ТҮРЕ	SPECIES
Proliferative and Inflammatory Lymphadenopath	ies		
Infectious		1	
Bacterial		Viral	_
Actinomyces spp.	D, C	Canine viral enteritides	D
Borrelia burgdorferi	D	Feline immunodeficiency virus	C
Brucella canis	D	Feline infectious peritonitis	C
Corynebacterium spp.	С	Feline leukemia virus	С
Mycobacteria	D, C	Infectious canine hepatitis	D
Nocardia spp.	D, C	Unclassified	
Streptococci	D, C	Pneumocystis carinii	D
Contagious streptococcal lymphadenopathy	С	Noninfectious	
Yersinia pestis	C	· · · · · · · · · · · · · · · · · · ·	
Bartonella spp.	D, C	Dermatopathic lymphadenopathy	D, C
Localized bacterial infection	D, C	Drug reactions	D, C
Septicemia	D, C	Idiopathic	D, C
Rickettsial		Distinctive peripheral lymph node hyperplasia	C
Ehrlichiosis	D, C	Plexiform vascularization of lymph nodes	С
Anaplasmosis	D, C	Immune-mediated disorders	
RMSF	D	Systemic lupus erythematosus	D, C
Salmon poisoning	D	Rheumatoid arthritis	Ď
Fungal	_	Immune-mediated polyarthritides	D, C
Aspergillosis	D, C	Puppy strangles	Ď
Blastomycosis	D, C	Other immune-mediated disorders	D, C
Coccidioidomycosis	D,	Localized inflammation	D, C
Cryptococcosis	D, C	Postvaccinal	D, C
Histoplasmosis	D, C		-, -
Phaeohyphomycosis	D, C	Infiltrative Lymphadenopathies	
Phycomycosis	D, C	Neoplastic	
Sporotrichosis	D, C D, C	Primary hemolymphatic neoplasms	
Other mycoses	D, C D, C	Leukemias	D, C
Algal	D, C	Lymphomas	D, C
Protothecosis Protothecosis	D, C	Malignant histiocytosis	D, C
Parasitic	D, C	Multiple myeloma	D, C
	Ь	Systemic mast cell disease	Ď, Č
Babesiosis	D	Metastatic neoplasms	-, -
Cytauxzoonosis	C D, C	Carcinomas	D, C
Demodicosis		Malignant melanomas	D, C
Hepatozoonosis	D	Mast cell tumors	D, C
Leishmaniasis	D	Sarcomas	D, C
Neospora caninum	D	our comes	<i>D</i> , <i>C</i>
Toxoplasmosis	D, C	Nonneoplastic	
Trypanosomiasis	D	Eosinophilic granuloma complex	C, D
		Mast cell infiltration (nonneoplastic)	D, C
		masi cen illinination (nonneopiasiic)	<i>D</i> , C

Modified from Hammer AS et al: Lymphadenopathy. In Fenner NR, editor: Quick reference to veterinary medicine, ed 2, Philadelphia, 1991, IB Lingingott

include the facial, retropharyngeal, mesenteric, and iliac (sublumbar) lymph nodes.

When evaluating dogs and cats with lymphadenopathy or diffuse splenomegaly, the clinician can glean important information from the history. Certain diseases have a defined geographic or seasonal prevalence, including leishmaniasis in the Mediterranean region of Europe, salmon poisoning in the Pacific Northwest, and some systemic mycoses, such as histoplasmosis in the Ohio River Valley. Systemic (constitutional) clinical signs are usually present in dogs with systemic mycoses, salmon poisoning, Rocky Mountain spotted fever (RMSF), ehrlichiosis, bartonellosis, leishmaniasis, and acute

D, Dogs; C, cats; RMSF, Rocky Mountain spotted fever.

leukemia. Clinical signs are rare or absent in dogs and cats with chronic leukemias, anaplasmosis, most lymphomas, and reactive lymphadenopathies occurring after vaccination; cats with idiopathic reactive lymphadenopathy (see the following section) are usually asymptomatic.

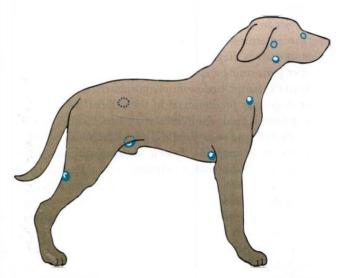


FIG 88-2

Anatomic distribution of clinically relevant lymph nodes in a dog. The nodes are in the same general location in cats. The lymph nodes depicted by the darkened circles include, from cranial to caudal, the mandibular, prescapular, axillary, superficial inguinal, and popliteal lymph nodes. The lymph nodes depicted by the open circles include, from cranial to caudal, the facial, retropharyngeal, and iliac or sublumbar lymph nodes. (Reprinted from Couto CG: Diseases of the lymph nodes and spleen. In Ettinger SJ, editor: Textbook of veterinary internal medicine—diseases of the dog and cat, ed 3, Philadelphia, 1989, WB Saunders.)

Clinical signs in dogs and cats with lymphadenopathy or splenomegaly are vague and nonspecific and are usually related to the primary disease rather than the organ enlargement; they include anorexia, weight loss, weakness, abdominal distention, vomiting, diarrhea, polyuria-polydipsia (PU/PD) (the latter in dogs with lymphoma-associated hypercalcemia), or a combination of these. Enlarged lymph nodes can occasionally result in obstructive or compressive signs (e.g., dysphagia resulting from enlarged retropharyngeal nodes, coughing resulting from enlarged tracheobronchial nodes, edema).

The distribution of the lymphadenopathy is also of diagnostic relevance. In patients with solitary or regional lymphadenopathy, the area drained by the lymph node(s) should be examined meticulously because the primary lesion is generally found there. Most cases of superficial solitary or regional lymphadenopathy in dogs and cats result from localized inflammatory or infectious processes or from metastatic neoplasia (less commonly), whereas most cases of deep (i.e., intraabdominal, intrathoracic) solitary or regional lymphadenopathy result from metastatic neoplasia or systemic infectious diseases (e.g., systemic mycoses). Most cases of generalized lymphadenopathy are caused by systemic fungal or bacterial infections (dogs), nonspecific hyperplasia (mainly cats), or lymphoma (dogs) (Table 88-2).

The characteristics of the lymph nodes on palpation are also important. In most dogs and cats with lymphadenopathy, regardless of the distribution, the lymph nodes are firm, irregular, and painless; their temperature is normal to the touch (cold lymphadenopathies); and they do not adhere to the surrounding structures. However, in patients with lymphadenitis the lymph nodes may be softer than usual and more tender and warmer than normal; they may also adhere to surrounding structures (fixed lymphadenopathy). Fixed



**TABLE 88-2** 

Correlation between Clinical Presentation and Etiology in Dogs and Cats with Lymphadenopathy in the Midwestern United States (in Relative Order of Importance)

PARTY STATES	SOLITARY/REGIONAL			
GENERALIZED	SUPERFICIAL	INTRACAVITARY		
Lymphoma	Abscess	Histoplasmosis (A, T)		
Histoplasmosis	Periodontal disease	Blastomycosis (T)		
Blastomycosis	Paronychia	Perianal gland adenocarcinoma (A)		
Postvaccinal	Deep pyoderma	Apocrine gland adenocarcinoma (A		
Anaplasmosis	Demodicosis	Primary lung tumors (T)		
Ehrlichiosis	Mast cell tumor	Lymphoma (A, T)		
Leukemias	Malignant melanoma	Mast cell tumor (A, T)		
Brucellosis	Eosinophilic granuloma complex	Prostatic adenocarcinoma (A)		
Systemic mast cell disease	Lymphoma	Malignant histiocytosis (A, T)		
Multiple myeloma		Lymphomatoid granulomatosis (T)		
Malignant histiocytosis		Tuberculosis (A, T)		
Systemic lupus erythematosus				
Other '				

lymphadenopathies may also be the presenting feature in dogs and cats with metastatic lesions, lymphomas with extracapsular invasion, or ceratin infectious diseases (e.g., mycobacteriosis).

The size of the affected lymph nodes is also important. Massive lymphadenopathy-lymph node size five to 10 times normal—occurs almost exclusively in dogs with lymphoma or lymphadenitis (lymph node abscess formation). In cats the syndrome of distinctive lymph node hyperplasia usually results in massive lymphadenopathy. Rarely, metastatic lymph nodes exhibit this degree of enlargement; the main example of massive metastatic lymphadenopathy is the apocrine gland adenocarcinoma metastases to the sublumbar lymph nodes. Recognizing that lymph nodes of normal size may contain metastatic neoplasia is important. Dogs with salmon poisoning may also have marked generalized lymphadenopathy as the presenting feature, preceded by or in conjunction with bloody diarrhea. Mild to moderate lymph node enlargement (two to four times the normal size) occurs mostly in a variety of reactive and inflammatory lymphadenopathies (e.g., ehrlichiosis, bartonellosis, anaplasmosis, RMSF, systemic mycoses, leishmaniasis, immunemediated diseases, skin diseases) and in leukemias.

As previously discussed, the area draining the enlarged lymph node(s) should always be thoroughly examined, paying particular attention to the skin, subcutis, and bone. In dogs and cats with generalized lymphadenopathy, evaluation of other hemolymphatic organs is important, including the spleen, liver, and bone marrow.

#### **SPLENOMEGALY**

#### **Etiology and Pathogenesis**

Splenomegaly is defined as a localized or diffuse splenic enlargement. The term *localized splenomegaly* (or splenic mass) refers to a localized, palpable enlargement of the spleen. Diffuse splenic enlargement occurs as a consequence of either the proliferation of normal cells or infiltration with normal or abnormal cells. Rarely, diffuse splenic enlargement can occur as a result of vascular changes (e.g., hyperemia, congestion). Focal splenomegaly is more common in dogs, and diffuse splenomegaly is more common in cats.

Diffuse splenomegaly is classified into four major categories in terms of its pathogenesis: lymphoreticular hyperplasia, inflammatory changes (i.e., splenitis), infiltration with abnormal cells (e.g., lymphoma) or substances (e.g., amyloidosis), and congestion (Table 88-3).

The spleen commonly reacts to blood-borne antigens and RBC destruction with hyperplasia of the MP/AP and lymphoid components. This hyperplasia has been referred to as work hypertrophy because it usually results in varying degrees of splenic enlargement. Hyperplastic splenomegaly is relatively common in dogs with ehrlichiosis, bacterial endocarditis, systemic lupus erythematosus, or chronic bacteremic disorders such as discospondylitis and brucellosis, and in cats with mycoplasmosis or immune-mediated cytopenias.

RBC phagocytosis by the splenic MP system in human beings has been recognized to lead to hyperplasia of this cell population, resulting in splenomegaly. The same seems to occur in dogs and cats with certain hemolytic disorders, including immune-mediated hemolytic anemia, druginduced hemolysis, pyruvate kinase deficiency anemia, phosphofructokinase deficiency anemia, familial nonspherocytic hemolysis in Poodles and Beagles, Heinz body hemolysis, and mycoplasmosis (see Chapter 83). Rarely, an area of focal splenomegaly is diagnosed histopathologically as hyperplasia after performing a splenectomy.

As in the lymph nodes, if polymorphonuclear leukocytes or macrophages predominate in the cellular infiltrate, the term *splenitis* is used. The infiltrates are also classified according to the cell type as *suppurative*, *granulomatous*, *pyogranulomatous*, or *eosinophilic*. *Splenic abscesses* can also form, often in association with a perforation by a foreign body. *Necrotizing splenitis* caused by gas-forming anaerobes can occur in dogs in association with splenic torsion or neoplasia. *Lymphoplasmacytic splenitis* cannot be distinguished cytologically from splenic hyperplasia. The etiologic agents for different types of splenitis are listed in Table 88-3.

Infiltrative splenomegalies are also common in small animals. Marked splenomegaly is a common finding in dogs and cats with acute and chronic leukemias (although it is more common in dogs), in dogs and cats with systemic mastocytosis, and in dogs with malignant histiocytosis. In addition, diffuse neoplastic infiltration of the spleen commonly occurs in dogs and cats with lymphoma and multiple myeloma. Diffuse splenomegaly may be the only physical examination and imaging finding in cats with monoclonal gammopathies; fine-needle aspiration (FNA) of the spleen reveals diffuse infiltration with plasma cells and is a common presentation for myeloma in this species. Metastatic splenic neoplasms usually result in focal splenomegaly but are rare.

Nonneoplastic causes of infiltrative splenomegaly are uncommon, with the exception of extramedullary hematopoiesis (EMH), which is more common in dogs than in cats. Because the spleen retains its fetal hematopoietic potential during adult life, a variety of stimuli-such as anemia, severe splenic or extrasplenic inflammation, neoplastic infiltration of the spleen, bone marrow hypoplasia, and splenic congestion-may cause the spleen to resume its fetal hematopoietic function and produce RBCs, white blood cells, and platelets. Finding EMH in percutaneous FNA of the spleen is extremely common in dogs and cats with diffuse or focal splenomegaly; the presence of hematopoietic blasts may lead to an erroneous diagnosis of lymphoma in some of these patients. I have also observed splenic EMH in dogs with pyometra, immune-mediated hemolysis, immune-mediated thrombocytopenia, several infectious diseases, and a variety of malignant neoplasms as well as in seemingly healthy dogs. Another disorder that commonly results in prominent infiltrative splenomegaly is the hypereosinophilic syndrome of cats (and some dogs, such as Rottweilers), a disease characterized by peripheral blood eosinophilia, bone marrow hyperplasia



**TABLE 88-3** 

Pathogenetic Classification of Splenomegaly in Dogs and Cats

ТҮРЕ	SPECIES	TYPE	SPECIES
Inflammatory and Infectious Splenomega Suppurative splenitis	ly	Pyogranulomatous splenitis	
Penetrating abdominal wounds Migrating foreign bodies Bacterial endocarditis Septicemia Splenic torsion Toxoplasmosis Infectious canine hepatitis (acute) Mycobacteriosis (i.e., tuberculosis)  Necrotizing splenitis Splenic torsion Splenic neoplasia Infectious canine hepatitis (acute) Salmonellasis	D, C D, C D, C D, C D, C D, C	Blastomycosis Sporotrichosis Feline infectious peritonitis Mycobacteriosis (i.e., tuberculosis) Bartonellosis  Hyperplastic Splenomegaly Bacterial endocarditis Brucellosis Discospondylitis Systemic lupus erythematosus Hemolytic disorders (see text)  Congestive Splenomegaly	D, C D, C D, C D, C D D, C D, C
Eosinophilic splenitis Eosinophilic gastroenteritis Hypereosinophilic syndrome	D, C C, D	Pharmacologic (see text) Portal hypertension Splenic torsion Infiltrative Splenomegaly	D, C D, C D
Lymphoplasmacytic splenitis Infectious canine hepatitis (chronic) Ehrlichiosis (chronic) Pyometra Brucellosis Hemobartonellosis Bartonellosis Leishmaniasis	D D, C D, C D, C D, C D, C	Neoplastic  Acute and chronic leukemias Systemic mastocytosis Malignant histiocytosis Lymphoma Multiple myeloma Metastatic neoplasia  Nonneoplastic	D, C D, C D, C D, C D, C D, C (rare)
Granulomatous splenitis Histoplasmosis Mycobacteriosis (i.e., tuberculosis) Leishmaniasis	D, C D, C D	EMH Hypereosinophilic syndrome Amyloidosis	D, C C, D D

Modified from Couto CG: Diseases of the lymph nodes and the spleen. In Ettinger S, editor: *Textbook of veterinary internal medicine*, ed 3, Philadelphia, 1989, WB Saunders.

of the eosinophil precursors, and multiple-organ infiltration by mature eosinophils (see Chapter 85).

The canine and feline spleens have a great capacity to store blood, and under normal circumstances they store between 10% and 20% of the total blood volume. However, tranquilizers and barbiturates can cause splenic blood pooling to increase by relaxing the smooth muscle of the splenic capsule, leading to congestive splenomegaly. The blood that has pooled in an enlarged spleen can account for up to 30% of the total blood volume. Anesthetics such as halothane also may result in marked decreases of 10% to 20% in the packed cell volume and plasma protein concentrations in dogs as a result of the same mechanism.

Portal hypertension can lead to congestive splenomegaly; however, such splenic congestion does not appear to be as common in dogs and cats as it is in human beings. Causes of portal hypertension that may lead to splenomegaly in small animals include right-sided congestive heart failure; obstruction of the caudal vena cava as a result of congenital malformations, neoplasia, or heartworm disease; and intrahepatic obstruction of the venae cavae. Splenic vein thrombosis is a common incidental finding in dogs; it is usually associated with administration of corticosteroids and is typically of no clinical relevance. Ultrasonographic evaluation in these patients usually reveals markedly distended splenic, portal, or hepatic veins or thrombi.

A relatively common cause of congestive splenomegaly in dogs is *splenic torsion*. Torsion of the spleen, either by itself or in association with gastric dilation-volvulus syndrome, commonly results in marked splenomegaly caused by

D, Dogs; C, cats; EMH, extramedullary hematopoiesis.

congestion. Splenic torsion can occur independently of gastric dilation-volvulus syndrome. Most affected dogs are of large, deep-chested breeds, primarily Great Danes and German Shepherd dogs. Clinical signs can be either acute or chronic. Dogs with acute splenic torsion are usually evaluated because of acute abdominal pain and distention, vomiting, depression, and anorexia. Dogs with chronic splenic torsion display a wide variety of clinical signs, including anorexia, weight loss, intermittent vomiting, abdominal distention, PU/PD, hemoglobinuria, and abdominal pain. Physical examination usually reveals marked splenomegaly, and radiographs typically reveal a C-shaped spleen. Ultrasonography of the abdomen in these patients may show greatly distended splenic veins. Hematologic abnormalities usually include regenerative anemia, leukocytosis with a regenerative left shift, and leukoerythroblastosis. Disseminated intravascular coagulation appears to be a common complication in dogs with torsion of the spleen. A high percentage of dogs with splenic torsion have hemoglobinuria, possibly as a consequence of intravascular or intrasplenic hemolysis. Dogs with splenic torsion and hemoglobinuria seen at our clinic occasionally have a positive direct Coombs tests. The treatment of choice for dogs with splenic torsion is splenectomy.

Splenic masses are more common than diffuse splenomegaly in dogs, whereas the opposite is true for cats. Most splenectomies in dogs are done to remove splenic masses. Because splenic masses in cats are extremely uncommon, the following discussion pertains primarily to localized splenomegaly in dogs.

Splenic masses can be classified according to their histopathologic features and biologic behavior as either neoplastic or nonneoplastic. Neoplastic splenic masses can be benign or malignant and mainly include hemangiomas (HAs) and hemangiosarcomas (HSAs), although the former are less common than the latter. Other neoplastic splenic masses that are occasionally found are leiomyosarcomas, fibrosarcomas, leiomyomas, myelolipomas, metastatic carcinomas or sarcomas, malignant histiocytic tumors, and occasionally lymphomas. Nonneoplastic splenic masses include primarily hematomas and abscesses, although splenic infarcts are occasionally described as splenic masses in dogs. As previously discussed, a splenic mass is occasionally diagnosed as a hyperplastic nodule on histopathology after splenectomy.

HSAs are malignant vascular tumors of the spleen; they are extremely common in dogs, constituting the most common primary neoplasm in surgically collected splenic tissues (i.e., splenectomy). These neoplasms are extremely rare in cats.

#### **Clinical Features**

The history-taking and physical examination in dogs with splenomegaly are similar to those in dogs with lymphade-nopathy. The clinical signs in dogs with splenomegaly are vague and nonspecific and include anorexia, weight loss, weakness, abdominal distention, vomiting, diarrhea, PU/PD, or a combination of these. PU/PD is relatively common in dogs with marked splenomegaly, particularly in those with

splenic torsion. Although the pathogenesis of the PU/PD is unclear, psychogenic polydipsia provoked by abdominal pain and distention of the splenic stretch receptors may be a contributory mechanism. Splenectomy in these dogs usually results in prompt resolution of the signs. Other signs associated with splenomegaly result from the hematologic consequences of the splenic enlargement and include spontaneous bleeding caused by thrombocytopenia, pallor caused by anemia, and fever caused by neutropenia or the primary disorder.

During a routine physical examination in pups and cats, the normal spleen is easily palpated as a flat structure oriented dorsoventrally in the left anterior abdominal quadrant. In some deep-chested dogs (e.g., Irish Setters, German Shepherd dogs), the normal spleen is also easily palpated during routine examination, either in the ventral midabdomen or in the left anterior quadrant. This is also the case in Miniature Schnauzers and in some Cocker Spaniels. The fullness of the stomach determines to what extent a normal spleen is palpable in other breeds of dogs. It is easily palpated postprandially because its contour conforms to the greater curvature of the stomach, such that it lies parallel to the last rib. However, not all enlarged spleens are palpable, and not every palpable spleen is abnormal. The characteristics of the spleen on palpation vary. In dogs an enlarged spleen can be either smooth or irregular ("lumpy-bumpy"). In most cats with marked splenomegaly, the surface of the organ is smooth; a diffusely enlarged, lumpy spleen in a cat suggests systemic mast cell disease. As previously discussed, animals with hematologic abnormalities secondary to splenomegaly may also have pallor, petechiae, or ecchymoses.

# APPROACH TO PATIENTS WITH LYMPHADENOPATHY OR SPLENOMEGALY

#### **Clinicopathologic Features**

A complete blood count (CBC) and a serum biochemistry profile should be obtained, particularly in dogs and cats with generalized or regional lymphadenopathies and those with diffuse splenomegaly. Changes in the CBC may indicate a systemic inflammatory process (e.g., leukocytosis with neutrophilia, left shift, monocytosis) or hemolymphatic neoplasia (e.g., circulating blasts in acute leukemia or lymphoma, marked lymphocytosis suggestive of chronic lymphocytic leukemia or ehrlichiosis). Occasionally the etiologic agent may be identified during examination of a blood smear (e.g., histoplasmosis, mycoplasmosis, trypanosomiasis, babesiosis). Polymerase chain reaction for clonality and immunophenotyping with flow cytometry are commonly used in our clinic in patients with lymphadenopathy or splenomegaly and circulating abnormal cells or lymphocytosis.

The spleen exerts a marked influence on the CBC, resulting in two patterns of hematologic changes in dogs and cats with splenomegaly: hypersplenism and hyposplenism, or

asplenia. Hypersplenism results from increased MP activity, is rare, and is characterized by cytopenias in the presence of a hypercellular bone marrow; these changes resolve after splenectomy. Hyposplenism is more common and results in hematologic changes similar to those seen in splenectomized animals, such as thrombocytosis, schistocytosis, acanthocytosis, Howell-Jolly bodies, and increased numbers of reticulocytes and nucleated RBCs.

Anemia in dogs and cats with lymphadenopathy or splenomegaly can occur as a result of the several mechanisms already mentioned. In brief, anemia of chronic disease can be seen in inflammatory, infectious, or neoplastic disorders; hemolytic anemia is usually present in patients with hemoparasitic lymphadenopathies or splenomegaly and in some dogs with malignant histiocytosis or hemophagocytic syndrome. Severe nonregenerative anemia may be seen in dogs with chronic ehrlichiosis, in cats with feline leukemia virusrelated disorders or feline immunodeficiency virus-related disorders, and in dogs and cats with primary bone marrow neoplasms (e.g., leukemias, multiple myeloma).

Thrombocytopenia is a common finding in patients with ehrlichiosis, RMSF, anaplasmosis, sepsis, lymphomas, leukemias, multiple myeloma, systemic mastocytosis, or some immune-mediated disorders. Pancytopenia is common in dogs with chronic ehrlichiosis or systemic immunemediated disorders; in dogs and cats with lymphoma or leukemia; and in cats with disorders associated with retroviral infections.

Two major serum biochemical abnormalities are of diagnostic value in dogs and cats with lymphadenopathy or diffuse splenomegaly: hypercalcemia and hyperglobulinemia. Hypercalcemia is a paraneoplastic syndrome that occurs in approximately 10% to 20% of dogs with lymphoma and multiple myeloma, although it may also occur in dogs with blastomycosis. It is extremely rare in cats with these diseases. Monoclonal hyperglobulinemia commonly occurs in dogs and cats with multiple myeloma and occasionally in dogs with lymphoma, ehrlichiosis, or leishmaniasis (see Chapter 89). Polyclonal hyperglobulinemia commonly occurs in dogs and cats with systemic mycoses; in cats with feline infectious peritonitis; and in dogs with ehrlichiosis, anaplasmosis, or leishmaniasis (see Chapter 89).

Serologic and microbiologic studies should always be conducted in dogs and cats with suspected infectious lymphadenopathy-splenomegaly. Serologic tests or polymerase chain reaction for canine ehrlichiosis, RMSF, brucellosis, and systemic mycoses may help diagnose regional or systemic lymphadenopathies. Lymph node specimens for bacterial and fungal cultures should also be obtained if necessary.

#### **Imaging**

Radiographic abnormalities in dogs with lymphadenopathy can be related to the primary disorder, or they can reflect the location and degree of lymphadenopathy. In general, plain radiographs or computed tomography (CT) are beneficial in dogs and cats with solitary lymphadenopathy to search for primary bone inflammation or neoplasia, in those with generalized peripheral (superficial) lymphadenopathy to detect intrathoracic or intraabdominal lymph node enlargement, and in those with deep regional lymphadenopathy involving the thoracic cavity to determine the distribution and size of the affected nodes and the changes in the pulmonary parenchyma and pleural space.

The spleen is normally well visualized on plain abdominal radiographs, but its appearance can vary widely. On dorsoventral or ventrodorsal views, the spleen is seen between the gastric fundus and the left kidney. The size and location of the spleen are more variable on lateral radiographs than on ventrodorsal or dorsoventral projections. In some breeds, such as Greyhounds, the spleen appears to be large on plain radiographs and ultrasonography. On plain radiographs, large splenic masses usually appear in the caudal abdomen or the midabdomen. Tranquilization or anesthesia usually results in a diffuse congestive splenomegaly, making radiographic interpretation of splenic size extremely difficult. CT is a useful diagnostic tool in dogs with focal or diffuse splenomegaly.

Ultrasonography is the noninvasive procedure of choice to evaluate intraabdominal lymphadenopathy and splenomegaly because it can accurately image and show the size of both enlarged lymph nodes and the spleen so that the patient's response to therapy can be monitored. In addition, ultrasound-guided FNA or biopsies can be performed with minimal complications. Abdominal ultrasonography can reveal diffuse splenomegaly, splenic masses, splenic congestion, hepatic nodules, or other changes; in addition, colorflow Doppler allows evaluation of splenic blood flow. A major issue a clinician frequently must deal with is the incidental splenic nodule in an older dog; these lesions are common and usually clinically irrelevant, but they tend to cloud the clinical picture in a patient with intraabdominal neoplasia. If possible, splenic nodules should be aspirated and evaluated cytologically. Of note, however, is that the presence of hepatic nodules in a dog with a splenic mass does not constitute a valid reason for an owner to decline treatment or request euthanasia because regenerative liver nodules are indistinguishable from metastatic lesions. Moreover, hypoechoic splenic nodules are frequently found in normal dogs.

Radionuclide imaging of the spleen (and less commonly of lymph nodes) using technetium-99m-labeled sulfur colloid has become an accepted method of splenic imaging in human beings and small animals. However, this technique only evaluates the spleen's ability to clear particulate matter and rarely provides a morphologic diagnosis.

#### **Additional Diagnostics**

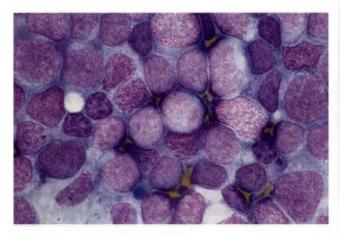
Evaluation of bone marrow aspirates or core biopsy specimens may be beneficial in dogs and cats with generalized lymphadenopathy or splenomegaly caused by hemolymphatic neoplasia or systemic infectious diseases. For example, acute or chronic leukemia in dogs may be difficult to diagnose on the basis of lymph node cytologic findings alone because the diagnosis is usually that of lymphoma (with the presence of well-differentiated or poorly differentiated lymphoid cells). In those cases, the combination of hematologic and bone marrow findings is usually diagnostic. Bone marrow evaluation should always be done before splenectomy in patients with cytopenias because the spleen may assume the primary hematopoietic function in dogs and cats with primary bone marrow disorders such as hypoplasia or aplasia. Splenectomy in these animals could remove the sole source of circulating blood cells, leading to death.

Cytologic evaluation of lymph node and splenic aspirates provides the clinician with a wealth of information and often constitutes the definitive diagnostic procedure in animals with lymphadenopathy or diffuse splenomegaly. In my experience, cytologic evaluation of appropriately collected specimens yields diagnostic findings in approximately 80% to 90% of dogs and 70% to 75% of cats with lymphadenopathy and in approximately 80% of dogs and cats with diffuse splenomegaly.

Although superficial lymph nodes can be aspirated with minimal difficulty, the successful aspiration of intrathoracic or intraabdominal lymph nodes or spleen requires some expertise and occasionally must be done under the guidance of imaging techniques (e.g., fluoroscopy, ultrasonography, CT) (see Chapter 75). To obtain an FNA of a superficial node, the area does not have to be surgically prepared. However, the aspiration of intrathoracic and intraabdominal structures (e.g., spleen) requires surgical preparation of the area and adequate restraint of the animal. Certain intraabdominal lymph nodes (e.g., markedly enlarged mesenteric or iliac nodes) are easily aspirated transabdominally by using manual isolation of the mass. Iliac lymph nodes can also be aspirated transrectally with a 2- to 3-inch (5 to 7.5 cm) needle. Splenic aspirates are obtained with the animal in right lateral or dorsal recumbency with manual restraint or mild sedation. Transabdominal splenic FNA in dogs or cats chemically restrained with phenothiazine tranquilizers or barbiturates usually yields blood-diluted specimens as a result of splenic congestion.

In a patient with generalized lymphadenopathy, the clinician must decide which lymph node to aspirate. Obviously aspiration of a node in which the tissue changes are representative of the ongoing disease is important. Therefore do not obtain a specimen from the largest lymph node because the central necrosis in such a node usually precludes a definitive diagnosis. Because clinical and subclinical gingivitis are common in older dogs and cats, mandibular lymph nodes should not be routinely aspirated because they are usually reactive and findings may obscure the primary diagnosis. The techniques of FNA are described in Chapter 75.

Several reviews of the cytologic evaluation of lymphoid tissues have appeared in the veterinary literature (see Suggested Readings). In brief, *normal lymph nodes* are composed primarily of small lymphocytes (80% to 90% of all cells); a low number of macrophages, medium or large lymphocytes,



Cytologic characteristics of a lymph node aspirate from a dog with massive generalized lymphadenopathy (lymphoma). Note a monomorphic population of large, round cells with a lacy chromatin pattern (neoplastic cells) intermixed with small, darker, normal lymphocytes. (Wright-Giemsa stain, ×1000.)

plasma cells, and mast cells can also be found. Normal spleens are similar except that RBCs are in high concentration given this organ's vascularity. Reactive lymph nodes and hyperplastic spleens are characterized by variable numbers of lymphoid cells in different stages of development (small, medium, and large lymphocytes; plasma cells); hematopoietic precursors are common in dogs and cats with splenic hyperplasia. The cytologic features of lymphadenitis-splenitis vary with the etiologic agent and the type of reaction elicited. Etiologic agents can frequently be identified in cytologic specimens from nodes with lymphadenitis. Metastatic neoplasms have different cytologic features depending on the degree of involvement and the cell type. Carcinomas, adenocarcinomas, melanomas, and mast cell tumors are easily diagnosed on the basis of cytologic findings. However, the cytologic diagnosis of sarcomas may be difficult because the neoplastic cells that comprise this tumor do not exfoliate easily. Primary lymphoid neoplasms (lymphomas) are characterized by a monomorphic population of lymphoid cells, which are usually immature (showing a fine chromatin pattern, one or more nucleoli, basophilic cytoplasm, vacuolation) (Fig. 88-3). For a more detailed description of cytologic changes, see Chapter 75.

When the cytologic examination of an enlarged lymph node or spleen does not yield a definitive diagnosis, excision of the affected node or incisional or even excisional splenic biopsy to obtain a specimen for histopathologic examination is indicated. Excision of the whole node is preferable because core biopsy specimens are difficult to interpret because the lymph node architecture is often poorly preserved. A wedge of tissue can be obtained during a splenic biopsy or, if the surgeon deems it necessary, a splenectomy can be performed. Care should be taken in handling the tissues during surgical manipulation because trauma may induce considerable artifactual changes, which would preclude interpretation of the

specimen. The popliteal lymph nodes are easily accessible and are the ones usually excised in dogs and cats with generalized lymphadenopathy.

Once a node is excised, it should be sectioned in half lengthwise, impression smears made for cytologic analysis, and the node fixed in 10% buffered formalin in a proportion of one part of tissue to nine parts of fixative. The specimen is then ready to be sent to a laboratory for evaluation. Samples can also be saved for cytochemical or immuno-histochemical evaluation, ultrastructural studies, or microbiologic evaluation, including polymerase chain reaction. The same guidelines apply to the preparation of splenic specimens.

# MANAGEMENT OF PATIENTS WITH LYMPHADENOPATHY OR SPLENOMEGALY

As previously discussed, no specific treatment exists for dogs or cats with local, regional, or generalized lymphadenopathy or diffuse splenomegaly. Treatment should be directed at the cause(s) of the lymphadenopathy or splenomegaly rather than at the enlarged lymph nodes or spleen. Exploratory celiotomies provide considerable information regarding the gross morphologic characteristics of an enlarged spleen and adjacent organs and tissues. However, direct visualization of these structures may be misleading because differentiation of some benign splenic masses (e.g., hematoma, HA) from their malignant counterpart (e.g., HSA) on the basis of gross morphology alone may be impossible. As discussed in the section on imaging, the surgeon may recommend to the owners that the animal be euthanized on the operating table because it has a splenic mass and nodules in the liver, only to find out that the hepatic nodules represent nodular hyperplasia or EMH and the primary mass was benign (e.g., HA or hematoma).

Splenectomy is indicated in the event of splenic torsion, splenic rupture, symptomatic splenomegaly, or splenic masses. The value of splenectomy is questionable in dogs with immune-mediated blood disorders, dogs and cats with splenomegaly caused by lymphoma in which chemotherapy has not induced splenic remission, and dogs and cats with leukemias. Splenectomy is contraindicated in patients with bone marrow hypoplasia in which the spleen is the main site of hematopoiesis.

Although rare, a syndrome of postsplenectomy sepsis has been documented in approximately 3% of dogs that undergo this surgical procedure in our clinic. The syndrome is similar to its human counterpart. Most dogs with postsplenectomy sepsis evaluated at our clinic were undergoing immunosuppressive therapy at the time of surgery or had undergone splenectomy for a neoplasm. This sepsis is usually rapid in onset (hours to days), so prophylactic bactericidal antibiotic therapy is recommended postoperatively. We routinely use cephalothin (20 mg/kg intravenously [IV] q8h) with or without enrofloxacin (5-10 mg/kg IV q24h) for 2 to 3 days

postoperatively. All dogs with clinically recognized postsplenectomy sepsis at our clinic have died within 12 hours of onset despite aggressive treatment.

The clinician occasionally encounters a patient in which the enlarged lymph node mechanically compresses or occludes a viscus, airway, or vessel. This may result in marked clinical abnormalities, such as intractable coughing, caused by tracheobronchial lymphadenopathy; colonic obstruction, caused by iliac lymphadenopathy; or anterior vena cava syndrome, caused by cranial vena cava and thoracic duct obstruction. Several treatment options are available for these situations. If the lymph node is surgically resectable, excision or drainage should be attempted. If the node is not surgically resectable or if surgery or anesthesia poses a high risk for the animal, one or more of the following can be used:

- Irradiation can shrink the lymph node and ameliorate the signs in animals with primary or metastatic neoplastic lesions. This can be accomplished by using intraoperative irradiation or external-beam fractionated therapy.
- Antiinflammatory doses of corticosteroids can be used (0.5 mg/kg PO q24h) in animals with fungal lesions such as *Histoplasma*-induced tracheobronchial lymphadenopathy.
- 3. Intralesional injections of corticosteroids (prednisolone, 50 to 60 mg/m²) can be successful in dogs and cats with solitary lymphomas or metastatic mast cell tumors if irradiation is not feasible.
- 4. Systemic antibiotic therapy may be beneficial in animals with solitary suppurative lymphadenitis.

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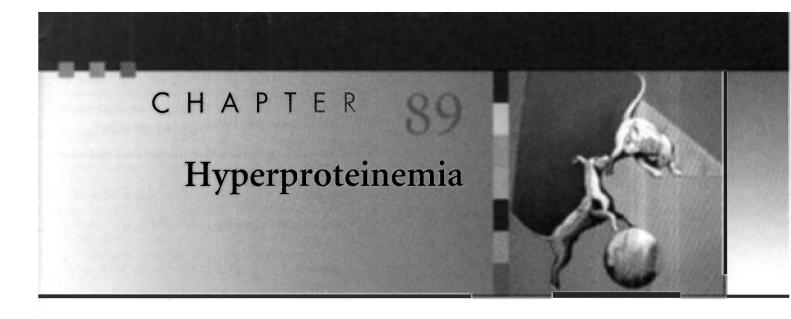
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The plasma protein fraction is composed mainly of albumin, globulins, and fibrinogen; fibrinogen is absent in serum as a result of clotting and conversion into fibrin. In some breeds, such as the Greyhound, serum protein concentrations are below the reference ranges for most laboratories (Fayos et al., 2005). *Hyperproteinemia* is the term given to an absolute or relative increase in the serum or plasma protein concentration. Before further evaluating a cat or dog with hyperproteinemia, the clinician should make sure that the condition is not attributable to a laboratory artifact (e.g., interference of other substances in protein determination), which constitutes one of the most common causes of "hyperproteinemia." Lipemia and, to a lesser degree, hemolysis typically result in artifactual increases in the plasma or serum protein concentration.

Once true hyperproteinemia has been established, the clinician should determine whether it is relative or absolute. Relative hyperproteinemia is usually accompanied by erythrocytosis and caused by hemoconcentration (i.e., dehydration). However, in an anemic cat or dog, relative hyperproteinemia may be present in association with a normal packed cell volume (i.e., the volume is low but hemoconcentration results in an artifactual increase). The relative proportions (ratio) of albumin and globulin provide considerable information regarding the pathogenesis of hyperproteinemia. This information is usually contained in reports of serum biochemistry profiles from most referral diagnostic laboratories and in-house analyzers. Occasionally only the total serum protein and serum albumin concentrations are reported. In this event, the total globulin concentration can be determined by simply subtracting the albumin concentration from the total protein concentration.

In dogs and cats with *relative hyperproteinemia* (i.e., hemoconcentration), both the albumin and globulin concentrations are increased above the reference values, whereas in those with *absolute hyperproteinemia* only the globulin concentration is increased, usually in association with a mild or marked decrease in the albumin concentration. Hyperalbuminemia does not occur because the liver is already at its maximal synthetic capacity. The finding of "hyperalbuminemia" and hyperglobulinemia indicates either the presence

of dehydration or a laboratory error. Rehydration results in resolution of relative hyperproteinemia.

When exposed to an electrical field (i.e., protein electrophoresis), the protein molecules migrate according to their shape, charge, and molecular weight. Staining of the electrophoresis gel after migration usually reveals six distinct protein bands: albumin (closer to the anode or negative electrode),  $\alpha_1$ -globulin,  $\alpha_2$ -globulin,  $\beta_1$ -globulin,  $\beta_2$ -globulin, and globulin (closer to the cathode or positive electrode) (Fig. 89-1, A). The albumin fraction is responsible for conferring oncotic properties on body fluids. Acute phase reactants (APRs), also referred to as acute phase proteins, migrate in the  $\alpha_2$  and  $\alpha_1$  regions, whereas immunoglobulins (Igs) and complement usually migrate in the and regions. Igs migrate in the following order (from anode to cathode and beginning in the  $\alpha_2$  region): IgA, IgM, and IgG. By evaluating a protein electrophoretogram, the clinician can gain insight into the pathogenesis of the hyperglobulinemia.

Increased production of globulins occurs in a variety of clinical situations, but mainly in two groups of disorders: inflammatory-infectious and neoplastic. In inflammation and infection the hepatocytes elaborate a variety of globulins, collectively termed APRs, which result in increases in the  $\alpha_2$ - and  $\alpha_1$ -globulin fractions. Because the hepatocytes are "reprogrammed" to produce APRs, the albumin production is "switched off," resulting in hypoalbuminemia. In conjunction with these changes, the immune system produces a variety of immune proteins (mainly Igs), which result in increases in the  $\alpha_2$ ,  $\beta$ , or  $\gamma$  regions or a combination of these.

Because the immune system reacts against an organism (e.g., a bacterium) by producing antibodies against each somatic antigen, several clones of lymphocytes—plasma cells are "instructed" to simultaneously produce specific antibody molecules (i.e., each clone is programmed to produce one specific antibody type against a specific antigen). As a consequence, immune stimulation leads to the appearance of a polyclonal band in the or regions or both. This polyclonal band is broad based and irregular and contains most of the Igs and complement generated by the immune cells. A typical inflammatory-infectious electrophoretogram therefore

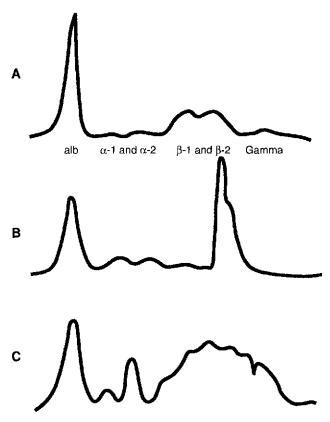


FIG 89-1

**A**, A normal canine or feline serum protein electrophoretogram. **B**, Electrophoretogram from a dog with multiple myeloma and a monoclonal gammopathy in the  $\beta_2\gamma$  region. Note the narrow spike approximately the same width as the albumin band. **C**, Electrophoretogram from a cat with feline infectious peritonitis and a typical polyclonal gammopathy. Note the  $\alpha_2$  spike (APRs) and the broad-based  $\beta$ - $\gamma$  spikes.

consists of a normal to mildly decreased albumin concentration and hyperglobulinemia resulting from increased  $\alpha_2$ -(i.e., APR) and  $\beta\gamma$ -globulins (polyclonal gammopathy) (Fig. 89-1, C).

Typical inflammatory-infectious electrophoretograms are seen in several common disorders, including chronic pyoderma, pyometra, and other chronic suppurative processes; feline infectious peritonitis; feline and canine hemobartonellosis and other hemoparasite infections; canine ehrlichiosis, anaplasmosis, and leishmaniasis; chronic autoimmune disorders (e.g., systemic lupus erythematosus, immune polyarthritis); and some neoplastic diseases, although they are rare (Box 89-1). Polyclonal gammopathies are also common in otherwise healthy old cats.

Monoclonal gammopathies occur when one clone of immune cells produces the same type and subtype of Ig molecule. Because these molecules are identical, they migrate in a narrow band (monoclonal spike, or M-component) located typically in the  $\beta$  or  $\gamma$  regions (Fig. 89-1, B). Monoclonal gammopathies occur in dogs with chronic multiple myeloma, lymphocytic leukemia, and lymphoma. They are



BOX 89-1

Diseases Associated with Polyclonal Gammopathies in Dogs and Cats

Infectious

Chronic pyoderma

Pyometra

Chronic pneumonia

Feline infectious peritonitis

Mycoplasmosis

**Bartonellosis** 

**Ehrlichiosis** 

Anaplasmosis

Leishmaniasis

Chagas' disease

**Babesiosis** 

Systemic mycoses

Immune-mediated diseases

Neoplasia

Lymphomas

Mast cell tumors

Necrotic or draining tumors

Common; uncommon.



BOX 89-2

Diseases Associated with Monoclonal Gammopathies in Dogs and Cats

Multiple myeloma

Chronic lymphocytic leukemia

Lymphoma

"Idiopathic" monoclonal gammopathy

Ehrlichiosis

Leishmaniasis

Feline infectious peritonitis

Chronic inflammation

also present in dogs with ehrlichiosis and occasionally in dogs with leishmaniasis and other chronic inflammatory disorders (Box 89-2). In most cats monoclonal gammopathies occur in association with multiple myeloma or lymphoma, but they can occur in cats with feline infectious peritonitis. Occasionally an M-component is detected in an otherwise asymptomatic cat or dog but additional evaluation fails to reveal a source for the monoclonal gammopathy. Although this likely represents the counterpart of human idiopathic monoclonal gammopathy, the patient should be reevaluated frequently for a clinically emerging malignancy. In cats the source of the M-component is usually the spleen, where a neoplastic population of well-differentiated plasma cells is frequently identified in asymptomatic cats with a monoclonal gammopathy.

The treatment of dogs and cats with monoclonal or polyclonal gammopathies is aimed at the primary disease. Refer to specific sections throughout this text for discussion of these treatments.

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#### CHAPTER

# Fever of Undetermined Origin



#### CHAPTER OUTLINE

FEVER OF UNDETERMINED ORIGIN

Disorders Associated with Fever of Undetermined Origin

Diagnostic Approach to the Patient with Fever of Undetermined Origin

#### **FEVER**

The term *fever* refers to a syndrome of malaise or nonspecific systemic clinical signs and pyrexia or hyperthermia. In this chapter, however, the terms *fever* and *pyrexia* are used interchangeably. Fever constitutes a protective physiologic response to both infectious and noninfectious causes of inflammation that enhances the host's ability to eliminate a noxious agent.

A variety of stimuli—including bacteria, endotoxins, viruses, immune complexes, activated complement, and necrotic tissue—trigger the release of endogenous pyrogens by the phagocytic system, mainly the mononuclear cells, or macrophages. These endogenous pyrogens include interleukin-1, tumor necrosis factor, and interleukin-6, among others. They activate the preoptic nucleus of the hypothalamus, raising the set point of the thermostat by generating heat through muscle contraction and shivering and conserving heat through vasoconstriction.

In human beings several patterns of fever have been associated with specific disorders; however, this does not appear to be the case in dogs and cats. In people with *continuous fever*, the pyrexia is maintained for several days or weeks. This type of fever is associated with bacterial endocarditis, central nervous system lesions, tuberculosis, and some malignancies. In people with *intermittent fever*, the body temperature decreases to normal but rises again for periods of 1 to 2 days; this is seen in brucellosis and some malignancies. In *remittent fever* the temperature varies markedly each

day but is always above normal (39.2° C); this type of fever is associated with bacterial infections. The term *relapsing* fever is used to refer to febrile periods that alternate with variable periods of normal body temperature, as seen in human beings with malaria.

#### FEVER OF UNDETERMINED ORIGIN

The term fever of undetermined (or unknown) origin (FUO) is used liberally in veterinary medicine to refer to a febrile syndrome for which a diagnosis is not evident. In human medicine, FUO refers to a febrile syndrome of more than 3 weeks' duration that remains undiagnosed after 1 week of thorough in-hospital evaluation. If the term FUO were to be used in the same way in animals as is recommended in human beings, few dogs and cats would actually have it. Therefore in this chapter the discussion focuses on the approach to a dog or cat with fever that does not respond to antibacterial antibiotic treatment and for which a diagnosis is not obvious after a minimal workup has been performed (e.g., complete blood count [CBC], serum biochemistry profile, urinalysis).

As a general rule, the clinician typically presumes that a dog or cat with fever has an infection until proved otherwise. This appears to be true in reality, as shown by the fact that a large proportion of dogs and cats with fever respond to nonspecific antibacterial treatment. No clinicopathologic evaluation is performed in most of these animals because the fever responds promptly to treatment.

## DISORDERS ASSOCIATED WITH FEVER OF UNDETERMINED ORIGIN

In human beings, certain infectious, neoplastic, and immunemediated disorders are commonly associated with FUO. Approximately one third of patients have infectious diseases; one third have cancer (mainly hematologic malignancies, such as lymphoma and leukemia); and the remaining third have immune-mediated, granulomatous, or miscellaneous disorders. In 10% to 15% of the patients with FUO, the underlying disorder remains undiagnosed despite intensive



#### Causes of FUO in Dogs and Cats

CAUSE	SPECIES AFFECTED	CAUSE	SPECIES AFFECTED
Infectious Bacterial		Immune Mediated	D C
Subacute bacterial endocarditis Brucellosis Tuberculosis Mycoplasmosis Plague Lyme disease Bartonellosis Suppurative infection {abscesses [liver, pancreas], stump pyometra, prostatitis, discospondylitis, pyelonephritis, peritonitis,	D D D, C C D D, C C	Polyarthritis Vasculitis Meningitis Systemic lupus erythematosus Immune hemolytic anemia Steroid-responsive fever Steroid-responsive neutropenia  Neoplastic Acute leukemia Chronic leukemia	D, C D D, C D, C D, C D, C
pyothorax, septic arthritis)  Rickettsial  Ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, salmon poisoning	D, C	Lymphoma Malignant histiocytosis Multiple myeloma Necrotic solid tumors	D, C D D, C D, C
Mycotic Histoplasmosis Blastomycosis Coccidioidomycosis	D, C D, C D	Miscellaneous  Metabolic bone disorders  Drug induced (tetracycline, penicillins, sulfa) Tissue necrosis Hyperthyroidism	D C, D D, C C, D
Viral Feline infectious peritonitis Feline leukemia virus infection Feline immunodeficiency virus infection	C C C	ldiopathic	D, C
Protozoal		The second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a second section in the second section in the second section is a section in the second section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the section in the section in the section is a section in the se	
Babesiosis Hepatozoonosis Cytauxzoonosis Chagas' disease Leishmaniasis	D D C D		

FUO, Fever of undetermined origin; D, dog; C, cat.

efforts. However, most of the review articles describing dogs and cats with FUO that have appeared in the literature extrapolate data from human papers.

On the basis of observations made in dogs and cats evaluated at our clinic and case reports in the literature, the most common cause of FUO appears to be infectious diseases, followed by immune-mediated, neoplastic disorders and miscellaneous (Table 90-1). However, despite aggressive evaluation, the cause of the fever cannot be determined in approximately 10% to 15% of small animals.

# DIAGNOSTIC APPROACH TO THE PATIENT WITH FEVER OF UNDETERMINED ORIGIN

A dog or cat with FUO should be evaluated in a systematic fashion. In general, a three-stage approach is used at our clinic (Box 90-1). The first stage consists of a thorough history-taking and physical examination as well as a minimal database. The second stage consists of additional noninvasive and invasive diagnostic tests. The third stage consists of a therapeutic trial, which is instituted if no diagnosis can be obtained after completion of the second stage.

# History and Physical Examination

When a febrile patient does not respond to antibacterial treatment, a course of action must be formulated. A thorough history should be obtained and a complete physical examination performed. The history rarely provides clues to the cause of the fever. However, a history of ticks may indicate a rickettsial or hemoparasitic disorder, previous administration of tetracycline (mainly to cats) may indicate a drug-induced fever, and travel to areas where systemic mycoses are endemic should prompt further investigation consisting of cytologic or serologic studies or fungal cultures.

During a physical examination the lymphoreticular organs should be evaluated because numerous infectious diseases affecting these organs (e.g., ehrlichiosis, Rocky Mountain spotted fever, bartonellosis, leukemia, systemic mycoses) may cause fever. An enlarged lymph node or spleen should be evaluated cytologically by using specimens



BOX 90-1

Diagnostic Evaluation of the Dog or Cat with FUO

#### First Stage

CBC

Serum biochemistry profile and thyroxine concentration Urinalysis

Urine bacterial culture and susceptibility

FNA of enlarged organs, masses, or swellings

#### Second Stage

Thoracic and abdominal imaging Echocardiography

Serial bacterial blood cultures

Immune tests (antinuclear antibody, rheumatoid factor)

Serum protein electrophoresis

Serologic tests or PCR (see Table 90-1)

Arthrocentesis (cytologic studies and culture)

Biopsy of any lesion or enlarged argan

Bone marrow aspiration (for cytologic studies and bacterial/fungal culture)

Cerebrospinal fluid analysis

Leukocyte or ciprofloxacin scanning

Exploratory celiotomy

#### Third Stage

Therapeutic trial (antipyretics, antibiotics, corticosteroids)

FUO, Fever of undetermined origin; CBC, complete blood count; FNA, fine-needle aspiration; PCR, polymerase chain reaction.

obtained by fine-needle aspiration (FNA). An FNA sample can also be obtained for bacterial and fungal culture and susceptibility testing if the cytologic studies reveal evidence of infection or inflammation. Any palpable mass or swelling should also be evaluated by using specimens obtained by FNA to rule out granulomatous, pyogranulomatous, and suppurative inflammation as well as neoplasia (see Chapter 75).

The clinician should thoroughly inspect and palpate the oropharynx, searching for signs of pharyngitis, stomatitis, or tooth root abscesses. The bones should also be thoroughly palpated, particularly in young dogs, because metabolic bone disorders such as hypertrophic osteodystrophy can cause fever associated with bone pain. Palpation and passive motion of all joints is also indicated in search of monoarthritis, oligoarthritis, or polyarthritis. A neurologic examination should be conducted to detect signs of meningitis or other central nervous system lesions. In older cats the ventral cervical region should be palpated to detect thyroid enlargement or nodules.

The thorax should be auscultated carefully in search of a murmur, which could indicate bacterial endocarditis. A thorough ocular examination may reveal changes suggestive of a specific cause (e.g., chorioretinitis in cats with feline infectious peritonitis or in dogs with monocytic ehrlichiosis).

# Clinicopathologic Evaluation

A minimum database consisting of a CBC, serum biochemistry profile, urinalysis, and urine bacterial culture and susceptibility testing should always be carried out in dogs and cats with persistent fever. The CBC may provide important clues regarding the cause of the fever (Table 90-2). A serum biochemistry profile rarely yields diagnostic information in dogs and cats with FUO, although it can provide indirect information on parenchymal organ function. However, the finding of hyperglobulinemia and hypoalbuminemia may indicate an infectious, immune-mediated, or neoplastic disorder (see Chapter 89). The finding of pyuria or white blood



TABLE 90-2

Hematologic Changes in Dogs and Cats with FUO

HEMATOLOGIC CHANGE	COMPATIBLE WITH
Regenerative anemia	Immune-mediated diseases, hemoparasites, drugs
Nonregenerative anemia	Infection, immune-mediated diseases, tissue necrosis, malignancy, endocarditis
Neutrophilia with left shift	Infection, immune-mediated diseases, tissue necrosis, malignancy, endocarditis
Neutropenia	Leukemia, immune-mediated diseases, pyogenic infection, bone marrow infiltrative disease drugs
Monocytosis	Infection, immune-mediated diseases, tissue necrosis, lymphoma, endocarditis, histiocytosis
Lymphocytosis	Ehrlichiosis, anaplasmosis, Chagas' disease, leishmaniasis, chronic lymphocytic leukemia
Éosinophilia	Hypereosinophilic syndrome, eosinophilic inflammation, lymphoma
Thrombocytopenia	Rickettsiae, leukemia, lymphoma, drugs, immune-mediated diseases
Thrombocytosis	Infections (chronic), immune-mediated diseases

cell casts in a urinalysis may indicate a urinary tract infection, which may be the cause of the FUO (i.e., pyelonephritis). Proteinuria associated with an inactive urine sediment should prompt the clinician to evaluate a urine protein/creatinine ratio to rule out glomerulonephritis or amyloidosis as the cause of the fever.

Other diagnostic tests that may be called for in patients with FUO are listed in Box 90-1. Echocardiography is indicated only if the patient has a heart murmur because it rarely detects a valvular lesion in dogs without murmurs. Some of the infectious diseases listed in Table 90-1 can be diagnosed on the basis of serologic findings or polymerase chain reaction testing.

Fluid from several joints should be aspirated for cytologic evaluation and possibly bacterial culture because polyarthritis may be the only manifestation of a widespread immunemediated disorder. Thoracic radiography and abdominal ultrasonography should be performed to search for a silent septic focus. In dogs and cats with neurologic signs associated with fever, a cerebrospinal fluid tap should be performed; in dogs, immune-mediated vasculitis or meningitis can cause marked temperature elevations. If a diagnosis has still not been reached, bone marrow aspirates for cytologic studies and bacterial and fungal culture should also be obtained. A leukocyte or ciprofloxacin scan may reveal a hidden septic focus. Finally, if a definitive diagnosis is ultimately not obtained, a therapeutic trial of specific antibacterial or antifungal agents or immunosuppressive doses of corticosteroids can be initiated.

# Treatment

If a definitive diagnosis is obtained, a specific treatment should be initiated.

The problem arises if the clinician cannot arrive at a definitive diagnosis. In these patients, changes in the CBC usually are the only clinicopathologic abnormality (see Table 90-2). That is, results of bacterial and fungal cultures, serologic tests, PCR, imaging studies, and FNAs are negative or normal. If the patient has already been treated with a broad-spectrum bactericidal antibiotic, a therapeutic trial of immunosuppressive doses of corticosteroids is warranted. However, before instituting immunosuppressive treatment, the owners should be informed of the potential consequences of this approach: primarily that a dog or cat with an undiagnosed

infectious disease may die as a result of systemic dissemination of the organism after the start of treatment. Dogs and cats undergoing a therapeutic trial of corticosteroids should be kept in the hospital and monitored frequently for worsening of clinical signs, in which case steroid therapy should be discontinued. In patients with immune-mediated (or steroid-responsive) FUO, the pyrexia and clinical signs usually resolve within 24 to 48 hours of the start of treatment.

If no response to corticosteroids is observed, two courses of action remain. In one, the patient can be released and given antipyretic drugs, such as aspirin (10 to 25 mg/kg PO q12h in dogs and 10 mg/kg PO q72h in cats) or other nonsteroidal antiinflammatories, and then returned to the clinic for a complete reevaluation in 1 to 2 weeks. Antipyretics should be used with caution, however, because fever is a protective mechanism and lowering the body temperature may be detrimental in an animal with an infectious disease. Moreover, drugs such as dipyrone and flunixin can result in marked hypothermia, which may have adverse effects. Also of note is that some nonsteroidal antiinflammatory drugs have ulcerogenic effects, can cause cytopenias, and may result in tubular nephropathy if the patient becomes dehydrated or receives other nephrotoxic drugs. The second course of action is to continue the trial of antibiotics by using a combination of bactericidal drugs (e.g., ampicillin and enrofloxacin) for a minimum of 5 to 7 days.

# Suggested Readings

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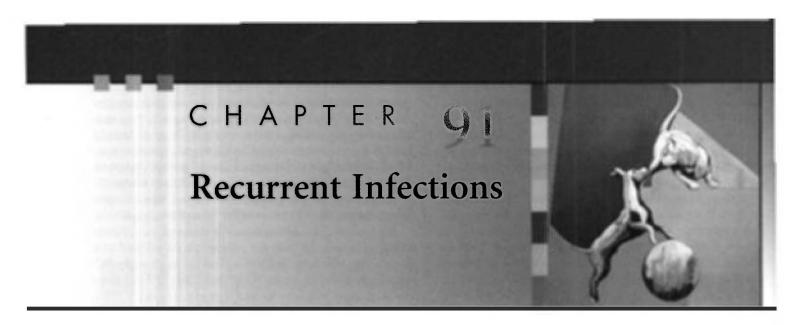
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Recurrent or persistent infections usually result from congenital or acquired abnormalities of the immune system. Although veterinary clinical immunology is not yet a well-developed specialty, great progress has been made over the past decade in elucidating the underlying immunologic abnormalities in dogs with recurrent infections. Most often these principles also apply to cats; however, with the exception of retrovirus-induced immunodeficiency syndromes and Chediak-Higashi syndrome, little is known about recurrent infections in this species.

## **Classification and Clinical Features**

Congenital immunodeficiency syndromes can affect the humoral, cellular, or phagocytic systems, either singly or in combination, and appear to be more common in dogs than in cats (Table 91-1). The molecular defects leading to these syndromes have been extensively investigated, and genetic testing for some of these syndromes is available. Humoral immunodeficiency syndromes usually result in recurrent upper and lower respiratory tract infections, dermatitis, and enteritis. Some Beagles with a selective immunoglobulin A (IgA) deficiency also have grand mal seizures of unknown pathogenesis and may be more susceptible to immunemediated diseases. Cellular immunodeficiency syndromes are apparently less common; a T-cell abnormality has been documented in Weimaraners with pituitary dwarfism and in Bull Terriers with lethal acrodermatitis (see Table 91-1). The disease in Weimaraner pups is characterized by retarded growth and recurrent respiratory and gastrointestinal tract infections. Necropsy findings in affected dogs include hypoplastic thymuses with no thymic cortex. Related Bull Terriers with growth retardation, progressive acrodermatitis, chronic pyoderma and paronychia, pneumonia, and diarrhea have significantly decreased lymphocyte blastogenesis in response to phytohemagglutinin stimulation. Other diseases that involve inconsistent cell- mediated immunologic abnormalities include Pneumocystis carinii infection in Dachshunds and systemic aspergillosis, generalized demodicosis, and protothecosis in other breeds. Bassett Hounds and Miniature Schnauzers have increased susceptibility to mycobacteriosis. Birman cats with congenital hypotrichosis and thymic atrophy resemble nude mice in that they are born hairless and have severe cell-mediated immune deficiency.

Abnormalities in the phagocytic system have been well documented in dogs and cats (see Table 91-1). They may occur as a consequence of decreased numbers of circulating phagocytes (e.g., in Grey Collies with cyclic hematopoiesis) or as a consequence of abnormal phagocytic function (e.g., defective neutrophil adhesion in Irish Setters with leukocyte adhesion deficiency, defective bactericidal capacity in Doberman Pinschers with recurrent respiratory tract infections). Occasionally the affected neutrophils are morphologically abnormal (e.g., Chediak-Higashi syndrome in Persian cats). Setters with a deficiency of surface adhesion proteins have recurrent episodes of omphalophlebitis, gingivitis, lymphadenitis, pyoderma, respiratory tract infections, pyometra, and fulminant sepsis. Affected Dobermans exhibit recurrent episodes of rhinitis and pneumonia that respond transiently to antibiotic therapy.

Immunodeficiency syndromes affecting more than one arm of the immune system (X-linked severe combined immunodeficiency syndrome) have been documented in Basset Hounds and Cardigan Welsh Corgis; they are associated with severe growth retardation and early death. Low serum IgG and IgA concentrations and abnormal lymphocyte blastogenesis in response to phytohemagglutinin are common in affected dogs; the defect is caused by a mutation in the gene that encodes for the interleukin-2 receptor.

Acquired immunodeficiency syndromes include canine distemper virus, parvovirus, and ehrlichial and Bartonella infections as well as generalized demodicosis in dogs and feline leukemia virus and feline immunodeficiency virus infections in cats. In addition, anticancer chemotherapy may cause variable degrees of immunosuppression.

#### **Diagnosis**

The type of infectious agent and the pattern of infection are usually determined by the nature of the defect. For example, defects in humoral immunity usually result in infections with pyogenic organisms affecting one or more sites. Defects in T-cell function result in viral, fungal, or protozoal infections that are usually widespread, and abnormalities



TABLE 91-1

#### Congenital Immunodeficiency Syndromes in Dogs and Cats

ARM	DEFECT	BREED
Humoral	IgA deficiency	Beagle, Shar-Pei, German Shepherd dog
	IgM deficiency	Doberman Pinscher?
	C3 deficiency	Brittany Spaniel
	Transient hypogammaglobulinemia	Samoyed
Cellular	Hypotrichosis, thymic atrophy, acrodermatitis	Weimaraner, Bull Terrier, Dachshunds?, Birman cats
Phagocytic	Cyclic hematopoiesis	Grey Collie
<b>U</b> ,	Abnormal granulation	Birman cat
	Chédiak-Higashi syndrome	Persian cat
	Mucopolysaccharidosis	Domestic short-haired cat, Siamese cat
	Defective neutrophil adhesion	Irish Setter
	Defective bactericidal capacity	Doberman Pinscher
	Abnormal chemiluminescence	Weimaraner
Combined	Severe combined immunodeficiency	Basset Hound, Cardigan Welsh Corgi

IgA, Immunoglobulin A; IgM, immunoglobulin M; C3, complement 3.

in the phagocytic system may result in skin, respiratory tract, meningeal, or systemic infections with pyogenic or enteric organisms. Therefore the type and pattern of the infection dictate which tests should be performed in these animals.

Several diagnostic tests can be used to evaluate dogs and cats with a suspected immunodeficiency syndrome. Some of these tests (i.e., neutrophil function tests, lymphocyte blastogenesis) require fresh blood samples (i.e., must be performed within 4 hours of sampling) and specialized laboratory equipment. They are therefore of limited use to general practitioners because such equipment is only available at teaching or research institutions. However, other tests can be performed on serum samples mailed to referral laboratories. Tests that can be used to evaluate animals with recurrent infections are listed in Table 91-2.

#### Management

The clinical management of these animals includes appropriate antimicrobial drugs determined on the basis of the etiologic agent identified (i.e., bacterial or fungal culture and sensitivity testing). If an infectious agent cannot be isolated and the animal appears to have a bacterial infection, bactericidal antibiotics that attain high intraleukocyte concentrations (e.g., sulfa-trimethoprim, enrofloxacin) should be used. Dogs and cats with suspected or known immunodeficiencies should be current on their vaccinations. If a severe immunodeficiency is present, the use of modified-live vaccines should be avoided because they may induce disease. Bone marrow transplantation and gene therapy with retroviral vectors have been used successfully in experimental dogs.

Nonspecific immunomodulators may be of benefit in dogs and cats with immunodeficiency. We have used levamisole (3 mg/kg PO two or three times per week) successfully in a limited number of dogs with recurrent infections;



**TABLE 91-2** 

Laboratory Diagnosis of Immunodeficiency Syndromes in Dogs and Cats

ARM	TESTS*
Humoral	Serum protein electrophoresis, immunoelectrophoresis, radial
	immunodiffusion for immunoglobulin
	concentrations, complement activity,
	immunophenotyping
Cellular	Lymphocyte blastogenesis, lymphocyte
	phenotyping, natural killer cell assays
Phagocytic	Nylon wool adhesion; migration under
0 /	agarose; phagocytosis of bacteria,
	yeasts, or latex; phagocytosis of
	opsonized particles; chemiluminescence;
	nitroblue tetrazolium reduction test;
	bacterial killing assay; flow cytometry

<sup>\*</sup>Molecular genetic testing is available for some of the conditions discussed.

however, because of the potential for toxicity in cats, this drug should be used with caution in this species.

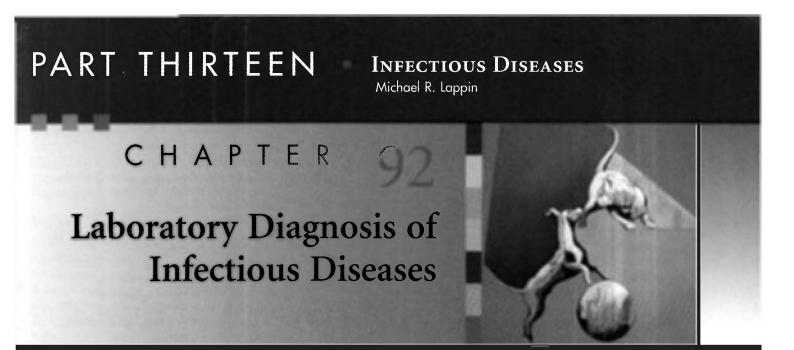
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# CHAPTER OUTLINE

#### DEMONSTRATION OF THE ORGANISM

Fecal Examination
Cytology
Tissue Techniques
Culture Techniques
Immunologic Techniques
Polymerase Chain Reaction
Animal Inoculation
Electron Microscopy
ANTIBODY DETECTION

Serum Body Fluids

Clinical syndromes induced by infectious agents are common in small animal practice. The combination of signalment, history, and physical examination findings are used to develop a list of differential diagnoses ranking the most likely infectious agents involved. For example, young, unvaccinated cats with conjunctivitis generally are infected by herpesvirus type 1, Chlamydophila felis, or Mycoplasma felis; if a dendritic ulcer is present, herpesvirus type 1 is most likely. Results of a complete blood count, serum biochemical panel, urinalysis, radiographs, or ultrasonography can also suggest infectious diseases. For example, a dog with polyuria, polydipsia, neutrophilic leukocytosis, azotemia, pyuria, and an irregularly marginated kidney on radiographic examination likely has pyelonephritis. After making a tentative diagnosis, the clinician then must determine whether to "test or treat." Empiric treatment is often satisfactory in simple, first-time infections of dogs or cats without life-threatening disease (see Chapter 93). However, having a definitive diagnosis is usually preferred so that treatment, prevention, prognosis, and zoonotic issues can be addressed optimally.

Documenting that the infectious agent is still present is the best way to make a definitive diagnosis. However, with some infectious agents, organism demonstration techniques have low sensitivity, are expensive, are invasive, are not adequately validated, or require specialized equipment. Antibody detection is commonly used to aid in the diagnosis of specific infectious diseases in these situations. Antibody detection is generally inferior to organism demonstration for three reasons: (1) antibodies can persist long after an infectious disease has resolved, (2) positive antibody test results do not confirm clinical disease induced by the infectious agent, and (3) in peracute infections, results of serum antibody tests can be negative if the humoral immune responses have not had time to develop. This chapter discusses the common organism demonstration and antibody detection techniques used in small animal practice.

## **DEMONSTRATION OF THE ORGANISM**

#### FECAL EXAMINATION

Examination of feces can be used to help diagnose parasitic diseases of the gastrointestinal (Table 92-1; see Chapter 29) and respiratory tracts (Table 92-2; see Chapter 20). The techniques used most frequently include direct and saline smear, stained smear, fecal flotation, and Baermann technique; each procedure can easily be performed in a small animal practice.

#### **Direct Smear**

Fresh, liquid feces or feces that contain large quantities of mucus should be microscopically examined immediately for the presence of protozoal trophozoites, including those of *Giardia* spp. (small-bowel diarrhea), *Tritrichomonas foetus* (large-bowel diarrhea), and *Pentatrichomonas hominis* (large-bowel diarrhea). A direct saline smear can be made to potentiate observation of these motile organisms.



**TABLE 92-1** 

# Demonstration Techniques for Canine and Feline Gastrointestinal Parasites

ORGANISM	FORM IN STOOL	SPECIES INFESTED*	OPTIMAL FECAL EXAMINATION TECHNIQUE
Cestodes			
Dipylidium caninum	Egg	В	Identification of adult
Echinococcus granulosa	Egg	Đ	Zinc sulfate centrifugation; other flotations
Echinococcus multilocularis	Egg	В	Zinc sulfate centrifugation; other flotations
Таепіа ѕрр.	Egg	В	Identification of adult
Protozoans			
Balantidium coli	Trophozoite	В	Direct or saline smear
	Cyst	D	Zinc sulfate centrifugation; other flotations
Cryptosporidium spp.†	Oocyst	В	Acid-fast or monoclonal antibody stain
Cystoisospora spp.	Oocyst	В	Sugar or zinc sulfate centrifugation
Entamoeba histolytica	Trophozoite	В	Direct or saline smear
·	Cyst	D	Zinc sulfate centrifugation; other flotations
Giardía spp.‡	Trophozoite	В	Direct or saline smear
• • • • • • • • • • • • • • • • • • • •	Cyst	В	Zinc sulfate centrifugation; other flotations
Toxoplasma gondii	Oocyst	В	Sugar or zinc sulfate centrifugation
Tritrichomonas foetus	Trophozoite	В	Direct or saline smear
	Cyst	D	Zinc sulfate centrifugation; other flotations
Flukes			
Eurytrema procyonis	Egg	· C	Fecal sedimentation
Nanophyetus salmincola	Egg	D	Fecal sedimentation
Platynosomum fastosum	Egg	С	Fecal sedimentation
Nematodes			
Ancylostoma spp.	Egg	В	Zinc sulfate centrifugation; other flotations
Ollulanus tricuspis	Egg	С	Zinc sulfate centrifugation; other flotations
Physaloptera spp.	Egg	В	Zinc sulfate centrifugation; other flotations
Spirocerca lupi	Egg	D	Zinc sulfate centrifugation; other flotations
Strongyloides stercoralis	Larvae	В	Baermann technique
Toxocara spp.	Egg	В	Zinc sulfate centrifugation; other flotations
Toxascaris spp.	Egg	В	Zinc sulfate centrifugation; other flotations
Trichuris vulpis	Egg	D	Zinc sulfate centrifugation; other flotations
Uncinaria stenocephala	Egg	В	Zinc sulfate centrifugation; other flotations

<sup>\*</sup> D, Dog; C, cat; B, dog and cat. † PCR and genotyping are available. ‡ Antigew assays, PCR, and genotyping are available.



**TABLE 92-2** 

# Demonstration Techniques for Common Canine and Feline Respiratory Tract Parasites

ORGANISM	FORM IN STOOL	SPECIES INFECTED*	OPTIMAL FECAL EXAMINATION TECHNIQUE
Aelurostrongylus abstrusus (lungworm)	Larva	C	Baermann technique
Andersonstrongylus milksi (lungworm)	Larva	D	Baermann technique
Eucoleus aerophila	Egg	D	Zinc sulfate or other flotations
Crenosoma vulpis (lungworm)	Egg	D	Zinc sulfate or other flotations
Eucoleus bohemi (nasal worm)	Egg	D	Zinc sulfate or other flotations
Filaroides hirthi (lungworm)	Larva	D	Baermann technique
Oslerus osleri (tracheal nodular worm)	Egg or larva	D	Zinc sulfate or other flotations and Baermann technique
Paragonimus kellicotti (lung fluke)	Egg	В	Fecal sedimentation
Pneumonyssoides caninum (nasal mite)	None	D	None; visualization of adults

<sup>\*</sup>D, Dog; C, cat; B, dog and cat.

A 2 mm  $\times$  2 mm  $\times$  2 mm quantity of fresh feces is mixed thoroughly with 1 drop of 0.9% NaCl or water. The surface of the feces or mucus coating the feces should be used because the trophozoites are most common in these areas. After application of a coverslip, the smear is evaluated for motile organisms by examining it under × 100 magnification.

#### Stained Smear

A thin smear of feces should be made from all dogs and cats with diarrhea. Material should be collected by rectal swab, if possible, to increase the chances of finding white blood cells. A cotton swab is gently introduced 3 to 4 cm through the anus into the terminal rectum, directed to the wall of the rectum, and gently rotated several times. Placing 1 drop of 0.9% NaCl on the cotton swab will facilitate passage through the anus and not adversely affect cell morphology. The cotton swab is rolled on a microscope slide gently multiple times to give areas with varying smear thickness (Fig. 92-1). After air drying, the slide can be stained. White blood cells and bacteria morphologically consistent with Campylobacter spp. (spirochetes) or Clostridium perfringens (spore-forming



Diff-Quik-stained fecal smear showing appropriate smear thickness.



FIG 92-2 Wright's-stained, thin fecal smear. A neutrophil and sporeforming rods are present in the center of the field.

rods; Fig. 92-2) can be observed after staining with Diff-Quik (Medion GmbH, Dudingen, Switzerland) or Wright's or Giemsa stains (see Cytology section). Histoplasma capsulatum or Prototheca may be observed in the cytoplasm of mononuclear cells. Methylene blue in acetate buffer (pH 3.6) stains trophozoites of the enteric protozoans. Iodine and acid methyl green stains are also used for the demonstration of protozoans. Modified acid-fast staining of a thin fecal smear can be performed in dogs and cats with diarrhea to aid in the diagnosis of cryptosporidiosis. Cryptosporidium spp. are the only enteric organisms of approximately 4 to 6 um in diameter that will stain pink to red with acid-fast stain (Fig. 92-3). Presence of neutrophils on rectal cytology can suggest inflammation induced by Salmonella spp., Campylobacter spp., or Clostridium perfringens; fecal culture is indicated in these cases, particularly if the history supports these differentials.

# **Fecal Flotation**

Cysts, oocysts, and eggs in feces can be concentrated to increase the sensitivity of detection. A variety of techniques are available for use in veterinary clinics. Centrifugation techniques are more sensitive than passive flotation techniques. Most eggs, oocysts, and cysts are easily identified after centrifugation in zinc sulfate solution (Box 92-1) or Sheather's sugar solution. These procedures are particularly superior to passive flotation techniques for the demonstration of protozoan cysts (particularly Giardia spp.; Fig. 92-4). Fecal sedimentation recovers most cysts and ova but also contains debris.

# **Baermann Technique**

This technique is used to concentrate motile larvae from feces. Some respiratory parasites are passed as larvated eggs but release larvae shortly after being passed in feces. Eggs or larvae from respiratory parasites can also be detected by cytologic evaluation of airway washings (Fig. 92-5).

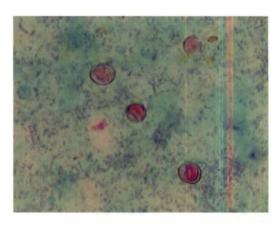


FIG 92-3 Cryptosporidium parvum oocysts stained with a modified acid-fast stain. The oocysts are approximately  $4 \times 6 \mu m$ .



BOX 92-1

# Zinc Sulfate Centrifugation Procedure

- Place 1 g fecal material in a 15-mL conical centrifuge tube.
- 2. Add 8 drops of Lugol iodine and mix well.
- Add 7 to 8 mL of zinc sulfate (1.18 specific gravity)\* and mix well.
- 4. Add zinc sulfate until there is a slight positive meniscus.
- 5. Cover the top of the tube with a coverslip.
- 6. Centrifuge at 1500-2000 rpm for 5 minutes.
- 7. Remove the coverslip and place on a clean microscope slide for microscopic examination.
- 8. Examine the entire area under the coverslip for the presence of ova, oocysts, or larvae at  $\times$  100.
- \* Add 330 g zinc sulfate to 670 mL distilled water.

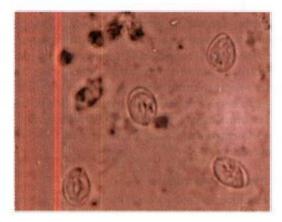


FIG 92-4 Giardia cysts after zinc sulfate flotation. The cysts are approximately  $10\times 8~\mu m$ .

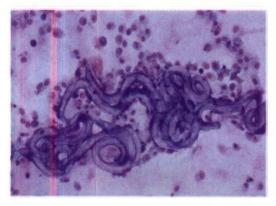


FIG 92-5
Aelurostrongylus abstrusus larvae in an airway washing collected by bronchoalveolar lavage. (Courtesy Dr. Timothy Hackett, Colorado State University, Fort Collins.)

#### **Preservation of Feces**

Feces should be refrigerated, not frozen, until assayed. If present, refrigerated *Toxoplasma gondii* oocysts will not likely sporulate and become infectious. In addition, refrigerated feces have less overgrowth of yeast, leading to fewer false-positive results. If a fecal sample is to be sent to a diagnostic laboratory for further analysis and will not be evaluated within 48 hours, it should be preserved. Polyvinyl alcohol, merthiolate-iodine-formalin, and 10% formalin preservation can be used. Ten percent formalin is commonly used because of its routine availability; the clinician should add 1 part feces to 9 parts formalin and mix well.

#### CYTOLOGY

Cytologic evaluation of exudates, bone marrow aspiration, blood smears, synovial fluid, gastric brushings, duodenal secretions, urine, prostatic washings, airway washings, fecal smears, tissue imprints, and aspiration biopsies is an inexpensive and extremely valuable tool for the documentation of infectious agents (Table 92-3). Cytologic demonstration of some infectious agents constitutes a definitive diagnosis. Morphologic appearance and Gram stain of bacteria aids in the selection of empiric antibiotics while waiting for results of culture and antimicrobial susceptibility testing (see Chapter 93).

For demonstration of most infectious agents, thin smears are preferred. Blood can be prepared as follows: 1 drop of blood approximately the size of a match head is placed at one end of a clean microscope slide. The short edge of another slide (i.e., spreader slide) is placed against the slide at a 30-degree angle and pulled back until the blood and the spreader slide make contact. After the blood spreads across the width of spreader slide, the slide is smoothly and quickly pushed away from the blood across the length of the slide ("push" smears). For materials other than blood, the spreader slide is laid gently on top of the material; the slides are then smoothly and rapidly pulled apart on parallel planes ("pull" smears). Cells in airway washings, prostatic washings, urine, aqueous humor, and cerebrospinal fluid (CSF) should be pelleted by centrifugation at 2000 g for 5 minutes before staining. For CSF the clinician should add 1 drop of 22% albumin or normal canine serum before centrifugation to help cells adhere to the slides. Multiple slides should always be made, if possible. After being placed on the microscope slide, the material is air dried at room temperature, fixed if indicated by the procedure used, and stained. Slides that are not stained immediately should be fixed by dipping in 100% methanol and air dried.

Cytologic specimens can be stained with routine stains; immunocytochemical techniques for certain pathogens are available (see Immunologic Techniques, p. 1287). Stains routinely used for the diagnosis of infectious diseases in small animal practice include Wright's-Giemsa stain, Diff-Quik, Gram stain, and acid-fast stain. Immunocytochemical techniques (e.g., fluorescent antibody staining of bone marrow cells for feline leukemia virus) are only performed in refer-



**TABLE 92-3** 

#### Characteristic Cytologic Morphology of Small Animal Bacterial and Rickettsial Agents

#### **AGENT MORPHOLOGIC CHARACTERISTICS** Bacteria Gram-positive, acid-fast-negative filamentous rod within sulfur granules Actinomyces spp. Usually occur in mixed morphologic groups Anaerobes Bacteroides fragilis Thin, filamentous, gram-negative rods Campylobacter spp. Seagull-shaped spirochete in feces Chlamydophila felis Large, cytoplasmic inclusions in conjunctival cells or neutrophils Clostridium spp. Large, gram-positive rods Clostridium perfringens Large, spore-forming rods in feces Hemoplasmas\* Rod or ring shaped on the surface of RBCs Tightly coiled spirochetes in gastric or duodenal brushinas Helicobacter spp. Mycobacterium spp. Intracytoplasmic acid-fast rods in macrophages or neutrophils Gram-positive, acid-fast-positive filamentous rod within sulfur granules Nocardia spp. Spirochetes in urine; darkfield microscopy required Leptospira spp. Yersinia pestis Bipolar rods in cervical lymph nodes or airway fluids Rickettsia Ehrlichia canis Clusters of gram-negative bacteria (morulae) in mononuclear cells Clusters of gram-negative bacteria (morulae) in neutrophils Ehrlichia ewingii Clusters of gram-negative bacteria (morulae) in neutrophils and eosinophils Anaplasma phagocytophilum Clusters of gram-negative bacteria (morulae) in platelets Anaplasma platys

ence or research laboratories (see Immunologic Techniques, p. 1287). The laboratory should be contacted for specific specimen handling information.

## **Bacterial Diseases**

Neorickettsia risticii

If bacterial disease is suspected, materials are collected aseptically and handled initially for culture (see Culture Techniques, p. 1287). After slides are prepared for cytologic evaluation, one is generally stained initially with Wright's-Giemsa or Diff-Ouik stain. If bacteria are noted Gram stain of another slide is performed to differentiate gram-positive and gram-negative agents. This information can be used to aid in the empiric selection of antibiotics (see Chapter 93). If filamentous, gram-positive rods are noted, acid-fast staining can help differentiate Actinomyces (not acid fast) from Nocardia (generally acid fast). If macrophages or neutrophils are detected, acid-fast staining is indicated to assess for Mycobacterium spp. within the cytoplasm. Bacteria can be present in small numbers, so failure to document organisms cytologically does not totally exclude the diagnosis. Bacterial culture of all samples with increased numbers of neutrophils or macrophages should always be considered. Some organisms such as Mycoplasma are rarely documented cytologically, whereas other organisms require special stains for optimal visualization. For some bacteria culture has never been successful. For example, the hemoplasmas of dogs

and cats (previously called *Haemobartonella felis* and *H. canis*) can be detected on the surface of red blood cells (RBCs) but have never been successfully cultured. Until the advent of PCR (see p. 1288), documentation of infection was based on cytology; Wright's-Giemsa stain is the best stain to use in practice for these organisms. The duration of parasitemia is short lived, and the organism commonly leaves the surface of the RBC if the blood is placed into ethylenediamine tetraacetic acid (EDTA), making it difficult to document the presence of the organism. Making thin blood smears immediately with blood that has not been placed into anticoagulant, or collecting blood into a heparinized syringe may help determine canine or feline hemoplasmas.

#### **Rickettsial Diseases**

Clusters of gram-negative bacteria (morulae) in mononuclear cells

Ehrlichia spp., Anaplasma spp., and Neorickettsia risticii (atypical ehrlichiosis) are occasionally found within the cytoplasm of cells in the peripheral blood, lymph node aspirates, bone marrow aspirates, or synovial fluid (see Chapter 96). Morulae of these genera can be found in different cell types (see Table 92-3). Wright's-Giemsa stain is superior to Wright's or Diff-Quik stain for the demonstration of morulae. Rickettsia rickettsii in endothelial cells lining vessels can be documented by immunofluorescent antibody staining (see Immunologic Techniques, p. 1287).

<sup>\*</sup> Previously known as Haemobartonella felis and H. canis. RBCs, Red blood cells.

# **Fungal Diseases**

Arthrospores and conidia of dermatophytes can be identified cytologically. Hairs plucked from the periphery of a lesion are covered with 10% to 20% potassium hydroxide on a microscope slide to clear debris. The slide is then heated, but not boiled, and examined for dermatophytes. All cats with chronic, draining skin lesions should have imprints of the lesions made and stained with Wright's-Giemsa stain followed by microscopic examination for the characteristic round, oval, or cigar-shaped yeast phase of *Sporothrix schenckii* within the cytoplasm of mononuclear cells (see Chapter 98). Periodic acid—Schiff stain is superior to Wright's-Giemsa stain for the demonstration of fungi. The cytologic appearance of the systemic fungi is presented in Table 98-1.

#### **Cutaneous Parasitic Diseases**

Cheyletiella spp., Demodex spp., Sarcoptes scabiei, Notoedres cati, and Otodectes cynotis are the most common small animal cutaneous parasites. Definitive diagnosis is based on cytologic demonstration of the organisms. Cheyletiella is demonstrated by pressing a piece of transparent tape against areas with crusts, placing the tape on a microscope slide, and examining it microscopically. Demodex spp. are most commonly detected in deep skin scrapings and follicular exudates; Cheyletiella spp., Sarcoptes scabiei, and Notoedres cati are detected in wide, more superficial scrapings. Otodectes cynotis or its eggs are detected in ceruminous exudates from the ear canals.

# **Systemic Protozoal Diseases**

The most common systemic protozoal diseases and the cytologic appearance and location of these agents are summarized in Table 92-4. Cytologic demonstration of these agents leads to a presumptive or definitive diagnosis of the disease. Wright's-Giemsa or Giemsa staining of thin blood films

should be used to demonstrate Leishmania spp., Trypanosoma cruzi, Babesia spp., Hepatozoon americanum, and Cytauxzoon felis. Collection of blood from an ear margin vessel may increase the chances of demonstrating the protozoans found in blood, particularly Babesia spp. and Cytauxzoon felis. Toxoplasma gondii and Neospora caninum cause similar syndromes in dogs, but their tachyzoites are difficult to distinguish morphologically; immunocytochemical staining or PCR is required to differentiate these agents. These protozoans can also be distinguished by evaluating for seroconversion because antibodies are specific to each agent. With the exception of T. gondii and N. caninum, systemic protozoans are rare or regionally defined in the United States. See Chapter 99 for further discussion of these agents.

#### Viral Diseases

Rarely, viral inclusion bodies are detected cytologically after staining with Wright's-Giemsa. Distemper virus infection causes inclusions in circulating lymphocytes, neutrophils, and erythrocytes of some dogs. Rarely, feline infectious peritonitis virus results in intracytoplasmic inclusions in circulating neutrophils. Feline herpesvirus 1 (FHV-1) transiently results in intranuclear inclusion bodies in epithelial cells.

#### TISSUE TECHNIQUES

Tissues collected from animals with suspected infectious diseases can be evaluated by several different techniques. Tissue samples should be aseptically placed in appropriate transport media for culture procedures or inoculated into laboratory animals, if indicated, before further handling.

Gently blotting the cut edge of the tissue on a paper towel to remove excess blood and then lightly touching the tissue multiple times to a microscope slide make tissue impressions for cytologic examination. Tissue specimens can then be



**TABLE 92-4** 

Characteristic Cytologic Morphology of Small Animal Systemic Protozoal Agents

AGENT	MORPHOLOGIC CHARACTERISTICS
Babesia canis	Paired piroplasms (2.4 $\times$ 5.0 $\mu$ m) in circulating RBCs
Babesia gibsoni	Single piroplasms (1.0 $\times$ 3.2 $\mu$ m) in circulating RBCs
Cytauxzoon felis	Piroplasms (1.0 $\times$ 1.5 $\mu$ m "signet ring" form; 1.0 $\times$ 2.0 $\mu$ m oval form; 1.0 $\mu$ m round form) in circulating RBCs; macrophages or monocytes of lymph node aspirates, splenic aspirates, or bone marrow
Hepatozoon canis and H. americanum	Gamonts in circulating neutrophils and monocytes
Leishmania spp.	Ovoid to round amastigates (2.5-5.0 µm × 1.5-2.0 µm) in macrophages found on imprints of exudative skin lesions, lymph node aspirates, or bone marrow aspirates
Neospora caninum	Free or intracellular (macrophages or monocytes) tachyzoites (5-7 $\mu$ m $ imes$ 1-5 $\mu$ m) in CSF, airway washings, or imprints of cutaneous lesions
Toxoplasma gondii	Free or intracellular (macrophages or monocytes) tachyzoites (6 × 2 μm) in pleural effusions, peritoneal effusions, or airway washings
Trypanosoma cruzi	Flagellated trypomastigates (one flagellum; 15-20 μm long) free in whole blood, lymph node aspirates, and peritoneal fluid

frozen, placed into 10% buffered formalin solution, or placed into glutaraldehyde-containing solutions. Frozen specimens are generally superior for immunohistochemical staining and PCR. Routine histopathologic evaluation is performed on formalin-fixed tissues. Special stains can be used to maximize the identification of some infectious agents. The clinician should alert the histopathology laboratory to the infectious agents most suspected to allow for appropriate stain selection. Glutaraldehyde-containing fixatives are superior to other fixatives for electron microscopic examination of tissues; this technique can be more sensitive than other procedures for demonstration of viral particles.

#### **CULTURE TECHNIQUES**

Bacteria, fungi, viruses, and some protozoans can be cultured. In general, a positive culture can be used to establish a definitive diagnosis. Bacterial culture can be combined with antimicrobial susceptibility testing to determine optimal drug therapy. Successful culture depends on collecting the optimal materials without contamination, transporting the materials to the laboratory as quickly as possible in the most appropriate medium to minimize organism death or overgrowth of nonpathogens, and using the most appropriate culture materials.

Culture results of body systems with normal bacterial and fungal flora, including the skin, ears, mouth, nasal cavity, trachea, feces, and vagina, are the most difficult to interpret. Finding positive culture results and inflammatory cells cytologically suggests the organism is inducing disease. Culture of a single agent, particularly if the organism is relatively resistant to antimicrobials, is more consistent with a diseaseinducing infection than if multiple, antibiotic-susceptible bacteria are cultured. Materials for routine aerobic bacterial culture can be placed on sterile swabs if the swabs remain moist and are placed on appropriate culture media within 3 hours of collection. If a delay of greater than 3 hours is expected, swabs containing transport medium should be used. These swabs should be refrigerated or frozen to inhibit bacterial growth if cultures are not to be started within 4 hours; some bacteria will grow more rapidly than others, potentially masking fastidious organisms. Most aerobes will survive at 4° C (routine refrigeration temperature) in tissue or on media-containing swabs for 48 hours. Solid-phase transport media that will support the growth of most aerobes, anaerobes, Mycoplasma spp., and fungi for several days if refrigerated are also routinely available. Routine aerobic culture is generally successful on fluid samples (e.g., urine, airway washings) stored at 20° C for 1 to 2 hours, 4° C for 24 hours, or 4° C for 72 hours if placed in transport medium.

Anaerobes can be successfully cultured from fluid collected aseptically into a syringe and the needle covered with a rubber stopper if the material is to be placed on culture media within 10 minutes of collection. Because of time limitations, transport media is generally required for samples from animals with suspected anaerobic infections. These media will support the growth of most anaerobes for 48 hours if stored at 4° C.

Samples for blood culture should be collected aseptically from a large vein after surgical preparation of the skin. In general, three 5-mL samples are collected over a 24-hour period in stable patients or at 1- to 3-hour intervals in septic patients. Unclotted whole blood is placed directly into transport media that will support the growth of aerobic and anaerobic bacteria, and it is incubated at 20° C for 24 hours. Culture for *Bartonella* spp. from the blood of dogs or cats is generally performed on a 1.5-mL whole blood sample collected aseptically and placed in an EDTA-containing tube (see Chapter 95).

Culture of feces for Salmonella spp., Campylobacter spp., and Clostridium perfringens is occasionally indicated in small animal practice. Approximately 2 to 3 g of fresh feces should be submitted to the laboratory immediately for optimal results; however, Salmonella and Campylobacter are usually viable in refrigerated fecal specimens for 3 to 7 days. To increase the likelihood of achieving positive culture results, a transport medium should be used if a delay is expected. The laboratory should be notified of the suspected pathogen so that appropriate culture media can be used.

Mycoplasma and Ureaplasma cultures are most commonly performed on airway washings, synovial fluid, exudates from chronic draining tracts in cats, urine from animals with chronic urinary tract disease, and the vagina of animals with genital tract disease. Samples should be transported to the laboratory in Amies medium or modified Stuart bacterial transport medium. Mycoplasma spp. culture should be specifically requested.

Mycobacterium spp. grow very slowly, and culture is often limited by overgrowth of other bacteria. Special medium is required; therefore the laboratory should be specifically instructed to culture for Mycobacterium spp. Tissue samples or exudates from animals with suspected Mycobacterium spp. infection should be refrigerated immediately after collection and transported to the laboratory as soon as possible. Exudates should be placed in transport media.

Cutaneous fungal agents can be cultured in the small animal office by using routinely available culture media. Materials from dogs or cats with suspected systemic fungal infection can be transported to the laboratory as described for bacteria, and the laboratory can be told specifically that fungal culture is needed. The yeast phase of the systemic fungi occurs in vivo and is not zoonotic; the mycelial phase of *Blastomyces*, *Coccidioides*, and *Histoplasma* grows in culture and will infect human beings. Thus in-house culture for these agents is not recommended.

Viral agents can be isolated from tissues or secretions at some laboratories. Contact the laboratory before submitting samples. Samples should be collected aseptically as for bacteria, placed in transport media, and immediately refrigerated to inhibit bacterial growth. The samples should be transported to the laboratory on cold packs but not frozen.

#### IMMUNOLOGIC TECHNIQUES

Infectious agents or their antigens can be detected in body fluids, feces, cells, or tissues by using immunologic techniques. In general, polyclonal or monoclonal antibodies against the agent in question are used in a variety of different test methods, including direct fluorescent antibody assay with cells or tissue, agglutination assays, and enzyme-linked immunosorbent assay (ELISA). Sensitivities and specificities vary by test but are generally high for most assays. Positive results with these tests generally prove infection; this is in contrast to antibody detection procedures, which only document exposure to an infectious agent. Contact the laboratory for details concerning specimen transport before collection.

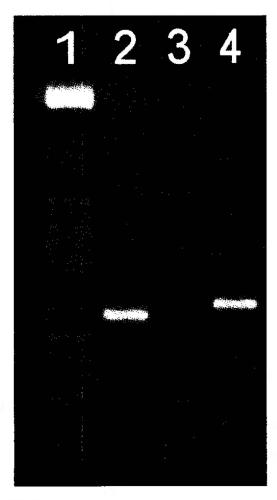
Commercially available assays are available for the detection of antigens of *Dirofilaria immitis*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, and FeLV in serum or plasma. The *Cryptococcus neoformans* latex agglutination procedure can also be performed on aqueous humor, vitreous humor, and CSF.

Parvovirus, *Cryptosporidium* spp., and *Giardia* spp. antigen detection procedures are available for use with feces. Parvovirus assays detect both canine and feline parvovirus antigen and may be affected transiently by administration of modified-live vaccines. Most *Giardia* antigen tests marketed for use with human feces and the test labeled for use with dog or cat feces detect the *Giardia* assemblages that infect dogs or cats. Samples are occasionally antigen positive but cyst negative on fecal flotation. In this situation whether the antigen test is falsely positive or the fecal flotation is falsely negative. None of the currently available *C. parvum* antigen tests marketed for use with human feces consistently detects *C. felis* or *C. canis* and should therefore not be used with feces from dogs and cats.

Immunocytochemistry and immunohistochemistry techniques are widely available for the documentation of a variety of infectious diseases. These procedures are particularly valuable for the detection of viral diseases, detection of agents present in small numbers, and for differentiation among agents with similar morphologic features. In general, these techniques are more sensitive and specific than histopathologic techniques and are comparable to culture. For example, focal feline infectious peritonitis granulomatous disease can be documented by immunohistochemical staining (see Chapter 97).

#### POLYMERASE CHAIN REACTION

PCR amplifies small quantities of DNA to detectable levels (Fig. 92-6). With a reverse transcriptase step, RNA is converted to DNA; therefore the technique can also be used to detect RNA (RT-PCR). In general PCR is much more sensitive than cytologic or histopathologic techniques and is comparable to culture and laboratory animal inoculation. PCR assays are of great benefit for documentation of infections, particularly if the organism in question is difficult to culture (e.g., Ehrlichia spp.) or cannot be cultured (e.g., hemoplasmas). Specificity can be quite high depending on the primers used in the reaction. For example, primers can be designed to detect one bacterial genus but not others. Primers can also be designed to identify only one species. For example, a PCR



Photograph of a PCR assay for hemoplasmas showing the two different band sizes that help differentiate species: Mycoplasma haemofelis (Lane 2) and Candidatus M. haemominutum (Lane 4). Lane 1 is a base pair ladder and Lane 3 is a negative sample. In this assay Candidatus M. turicensis is included in the M. haemofelis amplicon.

assay can be developed to detect all *Ehrlichia* spp. or just one species, such as *E. canis*.

Because of the inherent sensitivity of the reaction, PCR can give false-positive results if sample contamination occurs during collection or at the laboratory performing the procedure. False-negative results can occur if the sample is handled inappropriately; this is of particular importance for detection of RNA viruses by RT-PCR. Results may also be affected by treatment. Another potential problem is that no standardization exists among commercial laboratories offering PCR techniques; in addition, no external quality control exists (see Chapter 97).

Although PCR assays can be one of the most sensitive for documentation of infections, positive test results do not always prove that the infection is causing clinical illness. For example, because the technique detects DNA of both live and dead organisms, positive test results may be achieved even if the infection has been controlled. When the organism being

tested for commonly infects the background population of healthy pets, interpretation of results for a single animal can be difficult. For example, FHV-1 commonly infects cats and is commonly carried by healthy cats. Thus although PCR is the most sensitive way to document infection by FHV-1, the positive predictive value for disease of a FHV-1 PCR result is actually quite low. In one study more positive FHV-1 PCR results were detected in the healthy control group than in the group with conjunctivitis (Burgesser et al., 1999). In addition, the currently available PCR assays for FHV-1 also amplify modified-live vaccine strains, so a positive result does not even indicate presence of a pathogenic strain. Realtime PCR can be used to determine the amount of microbial DNA in a sample. The DNA load may correlate to the presence of disease for some agents. Because of these findings, small animal practitioners must carefully assess the predictive values of currently available PCR assays and the expertise and reliability of the laboratory that will be performing the assays. New PCR assays are being developed almost daily. See specific chapters for a discussion of the use of PCR for the detection of the agents.

## ANIMAL INOCULATION

Animal inoculation can be used to identify some infectious diseases. For example, oocysts of *Toxoplasma gondii* cannot be distinguished morphologically from those of *Hammondia hammondi* or *Besnoitia darlingi*; only *T. gondii* is infectious for human beings. *T. gondii* can be differentiated from the other coccidians by inoculation of sporulated oocysts into mice and monitoring for *T. gondii*—specific antibody production. However, because live animals are required, animal inoculation is rarely used in small animal practice.

#### **ELECTRON MICROSCOPY**

Flectron microscopy is a highly sensitive procedure for organism identification in body fluids and tissues. Glutaral-

dehyde-containing fixatives are used most commonly. One of the most clinically relevant uses of electron microscopy is for the detection of viral particles in feces of animals with gastrointestinal signs of diseases. Approximately 1 to 3 g of feces without fixative should be transported to the laboratory (e.g., Diagnostic Laboratory, Colorado State University, College of Veterinary Medicine and Biomedical Sciences, Fort Collins) by overnight mail on cold packs.

# ANTIBODY DETECTION

#### SERUM

A variety of different methods exists for detecting serum antibodies against infectious agents; complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, indirect fluorescent antibody assay (IFA), ELISA, and Western blot immunoassay are commonly used methods. Complement fixation, hemagglutination inhibition, serum neutralization, and agglutination assays generally detect all antibody classes in a serum sample. Western blot immunoassay, IFA, and ELISA can be adapted to detect specific immunoglobulin (Ig) M, IgG, or IgA responses.

Comparison of IgM, IgA, and IgG antibody responses against an infectious agent can be used to attempt to prove recent or active infection. In general, IgM is the first antibody produced after antigenic exposure (Fig. 92-7). Antibody class shift to IgG occurs in days to weeks. Serum and mucosal IgA immune responses have also been studied for some infectious agents, including *T. gondii*, feline coronaviruses, and *Helicobacter felis*.

Timing of antibody testing is important. In general, serum antibody tests in puppies and kittens cannot be interpreted as specific responses until at least 8 to 12 weeks of age because of the presence of antibodies from the dam passed to the

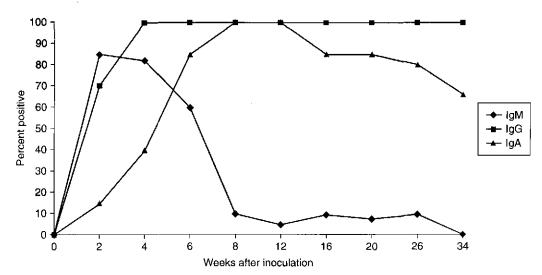


FIG 92-7
Serum Toxoplasma gondii lgM, lgG, and lgA immune responses after experimental inoculation in cats.

puppy or kitten in the colostrum. Most infectious agents can induce disease within 3 to 10 days after initial exposure; with many assays serum IgG antibodies are usually not detected until 1 to 2 weeks after initial exposure. On the basis of these facts, falsely negative serum antibody tests during acute disease can be common in small animal practice. If specific serum antibody testing is initially negative in an animal with acute disease, repeat antibody testing should be performed in 2 to 3 weeks to assess for seroconversion. Documentation of increasing antibody titers is consistent with recent or active infection. Assessment of both the acute and convalescent sera in the same assay on the same day is preferable to avoid interassay variation.

Sensitivity is the ability of an assay to detect a positive sample; specificity is the ability of an assay to detect a negative sample. Sensitivity and specificity vary with each assay. Positive predictive value is the ability of a test result to predict presence of disease; negative predictive value is the ability of a test result to predict absence of disease. Many of the infectious agents encountered in small animal practice infect a large percentage of the population, resulting in serum antibody production. However, they only induce disease in a small number of animals in the infected group. Examples include coronaviruses, canine distemper virus, T. gondii, Bartonella spp., and Borrelia burgdorferi. For these examples, even though assays with good sensitivity and specificity for the detection of serum antibodies are available, the predictive value of a positive test for presence of disease is extremely low. This is because antibodies are commonly detected in nondiseased animals. Diagnostic utility of some serologic tests is also limited because of the presence of antibodies induced by vaccination. Examples include feline coronaviruses, some B. burgdorferi assays, FHV-1, parvoviruses, FIV calicivirus, and canine distemper virus.

The clinician should interpret positive results in serum antibody tests only as evidence of present or prior infection by the agent in question. Recent or active infection is suggested by the presence of IgM, an increasing antibody titer over 2 to 3 weeks, or seroconversion (negative antibody result on the first test and positive antibody result on convalescent testing). However, detection of recent infection based on antibody testing does not always prove disease because of the agent in question. Conversely, failure to document recent or active infection based on serologic testing does not exclude a diagnosis of clinical disease. For example, many cats with toxoplasmosis develop clinical signs of disease after serum antibody titers have reached their plateau. The magnitude of antibody titer does not always correlate with active or clinical disease. For example, many cats with clinical toxoplasmosis have IgM and IgG titers that are at the low end of the titer scale; conversely, many healthy cats have IgG titers greater than 1:16,384 years after infection with T. gondii. The clinical diagnosis of an infectious disease usually includes the combination of the following:

- · Clinical signs referable to the agent
- · Serologic evidence of exposure to the agent

- · Exclusion of other causes of the clinical syndrome
- · Demonstration of the agent or response to treatment

#### **BODY FLUIDS**

Some infectious agents induce disease of the eyes or central nervous system (CNS). Documentation of agent-specific antibodies in aqueous humor, vitreous humor, or CSF can be used to support the diagnosis of infection of these tissues. Quantification of ocular and CSF antibodies is difficult to interpret if serum antibodies and inflammatory disease are present; serum antibodies leak into ocular fluids and CSF in the face of inflammation. Detection of local production of antibodies within the eye or CNS has been used to aid in the diagnosis of canine distemper virus infection, feline toxoplasmosis, and feline bartonellosis (see Chapters 95, 97, and 99). The following is a method to prove local antibody production by the eye or CNS:

Aqueous humor or CSF-specific antibody ×

Serum-specific antibody

Serum total antibody

Aqueous humor or CSF total antibody

A ratio greater than 1 suggests that the antibody in the aqueous humor or CSF was produced locally. This formula has been used extensively in the evaluation of cats with uveitis. Approximately 60% of cats with uveitis in the United States have *T. gondii*—specific IgM, IgA, or IgG values greater than 1 (see Chapter 99). The technique was also used to help prove that FHV-1 and *Bartonella henselae* are causes of uveitis in cats.

# Suggested Readings

Burgesser KM et al: Comparison of PCR, virus isolation, and indirect fluorescent antibody staining in the detection of naturally occurring feline herpesvirus infections, *J Vet Diagn Invest* 11:122, 1999

Dryden MW et al: Accurate diagnosis of *Giardia* spp and proper fecal examination procedures, *Vet Therapeutics* 7:4, 2006.

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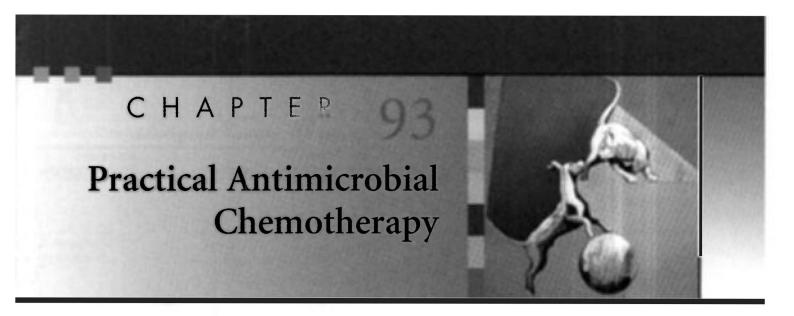
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Lappin MR et al: Bartonella spp. antibodies and DNA in aqueous humor of cats, Fel Med Surg 2:61, 2000.

Lappin MR et al: Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats, J Am Vet Med Assoc 220:38, 2002.



# CHAPTER OUTLINE

ANAEROBIC INFECTIONS
BACTEREMIA AND BACTERIAL ENDOCARDITIS
CENTRAL NERVOUS SYSTEM INFECTIONS
GASTROINTESTINAL TRACT AND HEPATIC
INFECTIONS
MUSCULOSKELETAL INFECTIONS
RESPIRATORY TRACT INFECTIONS
SKIN AND SOFT TISSUE INFECTIONS
UROGENITAL TRACT INFECTIONS

Antimicrobial drugs should only be administered if the index of suspicion for an infection exists. The prescribing veterinarian should also always be cognizant of the potential for development of antimicrobial resistance, particularly when prescribing drugs also used in human beings. Veterinarians should be familiar with judicious use of antimicrobial guidelines (http://www.aahanet.org/About\_aaha/AAFP\_AAHA\_AntimicrobialGuidelines.pdf).

In small animal practice, decisions to institute antimicrobial chemotherapy are almost always made without the benefit of results of culture and antimicrobial susceptibility testing. In simple, first-time infections, culture and antimicrobial susceptibility testing is often not performed. In life-threatening infections, decisions on the choice of antimicrobials must be made before obtaining the culture results; patient survival may depend on the selection of optimal treatment regimens. For some infectious agents such as *Ehrlichia* spp., *Borrelia burgdorferi*, *Rickettsia rickettsii*, and hemoplasmas, the organisms are not readily grown in culture and so empirical therapy is always used.

Recognition of the most common infectious agents (gram positive, gram negative, aerobic, or anaerobic) associated with infection of different organ systems or associated with different clinical syndromes is imperative in the empirical selection of antimicrobials. Cytologic findings and the results of a Gram stain can be used to identify microbes and

help choose appropriate antimicrobials. The antimicrobial selected must have an appropriate mechanism of action against the suspected pathogen and must achieve an adequate concentration in infected tissues. Bacteriostatic agents may be less effective for treatment of infections in immunosuppressed animals because normal immune responses are required for the drugs to have maximal effect (Table 93-1). The owner must be willing to administer the drug in the appropriate interval, and the drug must be affordable. Whether the antimicrobial has potential for toxicity is also an important consideration (Table 93-2). In animals with simple, first-time infections or when drugs with the potential for toxicity are used, the low end of the antimicrobial dose and the longest dosage interval should be used. Intracellular pathogens, anaerobic infections, and life-threatening infections, including bacteremia and central nervous system (CNS) infections, should be treated with the high end of the dose and the shortest dosage interval. In all animals with life-threatening infections, antibiotics should be administered parenterally for at least the first 3 to 5 days. Parenteral antibiotic administration is also indicated in animals with vomiting or regurgitation. Oral administration of antibiotics can be initiated when vomiting, regurgitation, or the lifethreatening condition have resolved.

Most simple, first-time infections in immunocompetent animals respond adequately to 7 to 10 days of antibiotic therapy. Therapy is generally continued for no more than 1 to 2 days past resolution of clinical signs. Chronic infections, bone infections, infections in immunosuppressed animals, infections resulting in granulomatous reactions, and those caused by intracellular pathogens are generally treated for a minimum of 1 to 2 weeks beyond resolution of clinical or radiographic signs of disease; the duration of therapy commonly exceeds 4 to 6 weeks.

When the results of antimicrobial susceptibility tests become available, the antibiotic choice is changed if indicated. If therapeutic response to an antibiotic in 72 hours is poor and an antibiotic-responsive infectious disease is still likely, an alternative treatment should be considered. Veterinarians should always know at least two classic drugs for each infectious agent (Tables 93-3 to 93-7).



Antibiotics Used for the Treatment of Bacterial Infections in Dogs and Cats and General Dosing Guidelines\*

Protein synthesis inhibition    DRUG	MECHANISM	BACTERIOSTATIC OR BACTERIOCIDAL	SPECIES	DOSAGE	ROUTE OF ADMINISTRATION	
Chloromphenical	Acetamides		Bacteriostatic			
Florfenical	Chloramphenicol			D C		
Aminoglycosides	Florfenical					
Amikacin  Amikacin  Amikacin  Amikacin  Amikacin  Amikacin  B			Bacteriocidal		<i>5</i> , 5, ,	•
B	Amikacin					
Neomycin   Corbamycin   Corbamycin   B   Company   Corbamycin   Corb	Gentamicin					
Cell wall synthesis inhibition						
Cell wall synthesis inhibition   Bacteriocidal synthesis inhibition   Bacteriocidal synthesis inhibition   Bacteriocidal synthesis inhibition   Cell wall synthesis inhibition   Cell wall synthesis inhibition   Cefadroxil (first generation)   C 22:35 mg/kg, q24h PO   PO   PO   PO   PO   PO   PO   PO						
Celadroxil (first generation)		synthesis	Bacteriocidal			,,
Cefadroxil (first generation)		synthesis	Bacteriocidal	В	3-10 mg/kg, q4-6h	IV, SC, IM
C   22-35 mg/kg, q24h   PO		inhibition		D	22-35 mg/kg, q12h	PO
Defipolation   Cefpolation   Ceftoding	generation			<u></u>	22.25 //2.4h	PC.
Cephalexin (first generation)   Separation   Separation						
Cefazolin (first generation)	Cephalexin (first			В		PO
Defixitin (second generation)   Cefixime (third generation)   Cefixime (third generation)   Cefotaxime (third generation)	Cefazolin (first			В	20-33 mg/kg, q6-	SC, IM, IV
Cefixime (thirid generation)         D         5-12.5 mg/kg, q12- 24h         PO           Cefotaxime (thirid generation)         B         20-80 mg/kg, q8- 3C, IM, IV           Ceftiofur Protein synthesis lincosamides         B acteriostatic         12h         SC           Macrolides/ lincosamides         Protein synthesis inhibition         Bacteriostatic         Frotein synthesis inhibition         D         5-10 mg/kg, q12- 24h         PO           Clarithromycin         B         5-10 mg/kg, q12- 24h         PO         PO           Clindamycin         D         5-20 mg/kg, q12- PO, SC, IV         PO, SC, IV           Erythromycin         B         10-25 mg/kg, q12- PO, SC           Lincomycin         B         11-22 mg/kg, q12- PO, IM, IV, SC           Tylosin         B         11-22 mg/kg, q12- PO, IM, IV, SC           Nitroimidazole         Protein synthesis inhibition         Bacteriocidal inhibition	Cefoxitin (second			В		SC, IM, IV
Cefotaxime (third generation)       B       20-80 mg/kg, q8- 12h       SC, IM, IV         Ceftiofur       Naxcel       B       2.2 mg/kg, q8h       SC         Macrolides/ lincosamides       Protein synthesis inhibition       Bacteriostatic inhibition       D       5-10 mg/kg, q12- 24h       PO         Azithromycin‡       D       5-15 mg/kg, q24h       PO       PO         Clarithromycin       B       5-10 mg/kg, q12h       PO         Clindamycin       D       5-20 mg/kg, q12h       PO         C       5-25 mg/kg, q12- 24h       PO       SC         Erythromycin       B       10-25 mg/kg, q8- PO       PO         Lincomycin Tylosin       B       11-22 mg/kg, q12h       PO, IM, IV, SC         Nitroimidazole       Protein synthesis inhibition       Bacteriocidal inhibition       D       10-25 mg/kg, q8- PO	Cefixime (third			D		PO
Naxcel	Cetotaxime (third			В	20-80 mg/kg, q8-	SC, IM, IV
Azithromycin‡  D	Ceftiofur		Bacteriostatic	В	2.2 mg/kg, q8h	SC
24h   C   5-15 mg/kg, q24h   PO	lincosamides	inhibition				
Clarithromycin       B       5-10 mg/kg, q12h       PO         Clindamycin       D       5-20 mg/kg, q12h       PO, SC, IV         C       5-25 mg/kg, q12- 24h       PO, SC         Erythromycin       B       10-25 mg/kg, q8- 12h       PO         Lincomycin       B       11-22 mg/kg, q12h       PO, IM, IV, SC         Tylosin       B       5-40 mg/kg, q12- 24h       PO         Nitroimidazole       Protein synthesis inhibition       Bacteriocidal inhibition       D       10-25 mg/kg, q8- PO	Azithromycin‡			D	24h	PO
Clarithromycin       B       5-10 mg/kg, q12h       PO         Clindamycin       D       5-20 mg/kg, q12h       PO, SC, IV         C       5-25 mg/kg, q12- 24h       PO, SC         Erythromycin       B       10-25 mg/kg, q8- 12h       PO         Lincomycin       B       11-22 mg/kg, q12h       PO, IM, IV, SC         Tylosin       B       5-40 mg/kg, q12- 24h       PO         Nitroimidazole       Protein synthesis inhibition       Bacteriocidal inhibition       D       10-25 mg/kg, q8-       PO				C	5-15 mg/kg, q24h	PO
C 5-25 mg/kg, q12- PO, SC 24h  Erythromycin  B 10-25 mg/kg, q8- PO 12h  Lincomycin  B 11-22 mg/kg, q12h PO, IM, IV, SC Tylosin  B 5-40 mg/kg, q12- PO  Nitroimidazole  Protein synthesis Bacteriocidal inhibition  Metronidazole§  D 10-25 mg/kg, q8- PO	Clarithromycin			В	5-10 mg/kg, q12h	
Erythromycin  B 10-25 mg/kg, q8- PO 12h  Lincomycin  B 11-22 mg/kg, q12h PO, IM, IV, SC Tylosin  B 11-22 mg/kg, q12h PO, IM, IV, SC Tylosin  B 5-40 mg/kg, q12- PO 24h  Nitroimidazole  Protein synthesis Bacteriocidal inhibition  Metronidazole§  D 10-25 mg/kg, q8- PO				D	5-20 mg/kg, q12h	
Lincomycin  Elincomycin  B  11-22 mg/kg, q12h  PO, IM, IV, SC  B  5-40 mg/kg, q12-  24h  Po  Nitroimidazole  Protein synthesis inhibition  Metronidazole§  D  10-25 mg/kg, q8-  PO					24h	
Tylosin B 5-40 mg/kg, q12- PO 24h  Nitroimidazole Protein synthesis Bacteriocidal inhibition  Metronidazole§ D 10-25 mg/kg, q8- PO	Erythromycin			В	10-25 mg/kg, q8- 12h	
Nitroimidazole     Protein synthesis inhibition     Bacteriocidal substitution       Metronidazole§     D     10-25 mg/kg, q8-     PO					5-40 mg/kg, q12-	
Metronidazole§ D 10-25 mg/kg, q8- PO	Nitroimidazole		Bacteriocidal			
	Metronidazole§			D		PO



Antibiotics Used for the Treatment of Bacterial Infections in Dogs and Cats and General Dosing Guidelines\*—cont'd

		BACTERIOSTATIC			ROUTE OF
DRUG	MECHANISM	OR BACTERIOCIDAL	SPECIES	DOSAGE	ADMINISTRATION
			С	10-25 mg/kg, q12- 24h	PO
			В	10 mg/kg, q8h	IV
Ronidazole			C	20-30 mg/kg, q12h	PO
Penicillins	Cell wall synthesis inhibition	Bacteriocidal		<i>0,</i> 0, 1	
Amoxicillin	IIIIIDIIIQII		В	10-22 mg/kg, q8- 12h	PO, SC, IM, IV
			С	50 mg/cat, q24h	PO
Amoxicillin and clavulanate			D	12.5-22 mg/kg, q8- 12h	PO
			C	62.5 mg, q8-12h	PO
Ampicillin sodium			В	20-40 mg/kg, q8- 12h	SC, IM, IV
Dicloxacin			В	25 mg/kg, q6-8h	PO
Oxacillin			В	22-40 mg/kg, q8h	PO, SC, IM, IV
Penicillin G			В	20,000 Ŭ/kg, qó-8h	PO, IM, IV
Ticarcillin and clavulanate			D	20-50 mg/kg, q6-8h	IM, IV, SC
Quinolones	Nucleic acid inhibition	Bacteriocidal			
Ciprofloxacin			D	10-20 mg/kg, q24h	PO
'			С	5-15 mg/kg, q24h	PO
Difloxacin			D	5 mg/kg, q24h	PO
Enrofloxacin			D	5-20 mg/kg, q12- 24h	PO, IM, SC, IV
			C	5.0 mg/kg, q24h	PO, IM
Marbofloxacin			В	2.75-5.5mg/kg, q24h	PO
Orbafloxacin			D	2.5-7.5 mg/kg, q24h	PO
			С	2.5 mg/kg, q24h	PO
Potentiated sulfas	Intermediary metabolism inhibition	Bacteriocidal			
Ormetoprim- sulfadimethoxine	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		D	55 mg/kg, q24h day 1, then 27.5 mg/	PO
Trimethoprim-			В	kg, q24h 15-30 mg/kg, q12h	PO
sulfonamide Tetracyclines	Protein synthesis inhibition	Bacteriostatic			
Doxycycline¶	mmomon		В	5-10 mg/kg, q12h	PO, IV
Minocycline			В	5-12.5 mg/kg, q12h	PO, IV
Tetracycline			В	22 mg/kg, q8-12h	PO

IM, Intramuscular; IV, intravenous; SC, subcutaneous; PO, oral; D, dog; C, cat; B, dog and cat.

<sup>\*</sup>The dose ranges and intervals in this table are general. Please see appropriate sections to determine the optimal dose for specific syndromes or infections.

<sup>†</sup> For parenterally administered aminoglycosides, giving the total daily dose at one time may lessen the potential for renal toxicity.

<sup>‡</sup> For simple infections azithromycin can be given daily for 3 days and then every third day.

<sup>§</sup>The maximal total daily dose should be 50 mg/kg.

<sup>¶</sup>The drug can be given once daily to cats for the treatment of simple infections.



**TABLE 93-2** 

#### Common Antibiotic Toxicities

TOXICITY	ANTIBIOTIC EXAMPLES
Aminoglycosides	Renal tubular disease
	Neuromuscular blockade
T:	Ototoxicity
Cephalosporins	Immune-mediated diseases
Chloramphenicol	Bone marrow/aplastic anemia
	(predominantly cats)
	Inhibition of drug metabolism
Doxycycline	Esophagitis or strictures in cats
	given tablets or capsules
Macrolides/	Vomiting or diarrhea
lincosamides	Cholestasis
	Esophagitis or strictures in cats
No. 1 1	given clindamycin capsules
Nitroimidazoles	Neutropenia (metronidazole)
	CNS toxicity (metronidazole and
Penicillins	ronidazole)
Quinolones	Immune-mediated diseases
Guinolones	Failure of cartilage development in young, growing animals
	Retinal dysfunction in some cats
	with some formulations
	Potentiation of seizures
Sulfonamides	Hepatic-cholestasis or acute hepatic
obilonamaes	necrosis (rare)
	Macrocytic anemia (long-term
	administration in cats)
	Thrombocytopenia
	Suppurative, nonseptic polyarthritis
	(predominantly Doberman)
	Keratoconjunctivitis sicca
	Renal crystalluria (rare)
Tetracyclines	Renal tubular disease
	Cholestasis
	Fever, particularly in cats
	Inhibition of drug metabolism

CNS, Central nervous system.

Conditions resulting in devitalized, granulomatous, or consolidated tissues, such as aspiration pneumonia, may not show radiographic signs of improvement before 7 days. Devitalized tissues should be debrided, if possible, to aid in the resolution of infection.

The following is a brief discussion of the empirical antimicrobial choices for treatment of infections of various body systems or types of infections. The reader is referred to individual chapters for further information concerning adjunct treatments.

# ANAEROBIC INFECTIONS

The anaerobic bacteria of clinical significance in dog and cats are Actinomyces spp., Bacteroides spp., Clostridium spp.,



**TABLE 93-3** 

Empirical Antibiotic Choices for Dogs and Cats with Cutaneous and Soft Tissue Infections

INFECTIOUS AGENT	ANTIBIOTIC CHOICES
	a a selle a alle
Abscesses (anaerobes)	1. Ampicillin, amoxicillin,
	amoxicillin-clavulanate
	2. Clindamycin
	3. Metronidazole
	4. Chloramphenicol
	5. First- or second-generation
	cephalosporins
Actinomyces	1. Penicillins
	2. Clindamycin
	3. Erythromycin
	<ol><li>Chloramphenicol</li></ol>
	<ol><li>Minocycline</li></ol>
Gram-negative or	<ol> <li>Quinolones</li> </ol>
resistant pyoderma	
L-form bacteria	<ol> <li>Doxycycline</li> </ol>
	2. Erythromycin
	<ol><li>Chloramphenicol</li></ol>
Nocardia	<ol> <li>Penicillins (high dose)</li> </ol>
	<ol><li>Penicillins combined with</li></ol>
	potentiated sulfas for
	penicillin-resistant Nocardia
	3. Minocycline
	4. Erythromycin
	5. Amikacin
	6. Imipenem
Rapidly growing	1. Doxycycline or minocycline
Mycobacterium	2. Quinolones
,	3. Potentiated sulfas
	4. Aminoglycosides
	5. Clarithromycin
Staphylococcal	1. First-generation
pyoderma	cephalosporin
p/	Amoxicillin-clavulanate or
	dicloxacillin or cloxacillin or
	oxacillin
	3. Clindamycin or lincomycin
	or erythromycin
	4. Trimethoprim-sulfadiazine or
	ormetoprim-sulfadimethoxine
	(superficial pyoderma)

Eubacterium spp., Fusobacterium spp., Peptostreptococcus spp., and Porphyromonas spp. Actinomyces is a facultative anaerobe; the other organisms are obligate anaerobes, which cannot use oxygen metabolically and die in its presence. Anaerobic bacteria are part of the normal flora in areas with low oxygen tension and low oxygen-reduction potential, such as the mucous membranes of the oral cavity and vagina. The origin of most anaerobic infections is the animal's own flora. Anaerobic infections are potentiated by poor blood supply, tissue necrosis, prior infection, or immunosuppression. Anaerobic bacteria produce a number of enzymes and factors that induce tissue injury and promote colonization.



**TABLE 93-4** 

Empirical Antibiotic Choices for Dogs and Cats with Cardiopulmonary Infections

ORGAN SYSTEM OR INFECTIOUS AGENT	ANTIBIOTIC CHOICES
Bacterial pneumonia	1. Amoxicillin-clavulanate
	<ol><li>Potentiated sulfas</li></ol>
	3. First-generation
	cephalosporin
Danka Salaman arang	4. Chloramphenicol
Bacterial pneumonia with bacteremia*	<ol> <li>Enrofloxacin and penicillin (or ampicillin or amoxicillin</li> </ol>
willi baciereilia	or clindamycin or
	metronidazole or first-
	generation cephalosporin)
	2. Imipenem
Bacteremia, sepsis, and	1. Enrofloxacin and penicillin
bacterial endocarditis	(or ampicillin or amoxicillin
	or clindamycin or first-
	generation cephalosporin)
	Aminoglycoside and
	penicillin (or ampicillin or
	amoxicillin or clindamycin
	or first-generation
	cephalosporin)  3. Second- or third-generation
	cephalosporin
	4. Imipenem
	5. Ticarcillin and clavulanate
Pyothorax*	1. Penicillin derivatives
,	2. Clindamycin
	<ol><li>Metronidazole</li></ol>
	<ol><li>Chloramphenicol</li></ol>
	5. First-generation
T 1 . /	cephalosporins
Toxoplasmosis/	1. Clindamycin
neosporosis Upper respiratory	Potentiated sulfas     Amoxicillin or amoxicillin-
Opper respiratory	clavulanate
	2. First-generation
	cephalosporin
	3. Potentiated sulfas
	4. Clindamycin
	<ol><li>Doxycycline†</li></ol>
	6. Chloramphenicol†
	7. Quinolone†

<sup>\*</sup>Generally mixed infections, often with gram-negative, grampositive, aerobic, and anaerobic combinations. If signs of bacteremia or sepsis are present, use a four-quadrant antibiotic choice administered parenterally as discussed for sepsis until culture and antimicrobial susceptibility testing results return. † Should be used if Bordetella, Mycoplasma, or Chlamydophila are suspected.



**TABLE 93-5** 

Empirical Antibiotic Choices for Dogs and Cats with Hepatic and Gastrointestinal Infections

INFECTIOUS AGENT	ANTIBIOTIC CHOICES
Bacterial cholangiohepatitis	Amoxicillin or amoxicillin clavulanate     First-generation cephalosporin
Bacterial overgrowth	<ol> <li>Metronidazole</li> <li>Quinolones</li> <li>Penicillin derivative</li> <li>Metronidazole</li> <li>Tylosin</li> </ol>
Campylobacter spp.	<ol> <li>Tetracycline derivative</li> <li>Erythromycin</li> <li>Quinolone</li> </ol>
Clostridium perfringens	<ol> <li>Chloramphenicol</li> <li>Penicillin derivative</li> <li>Tylosin</li> </ol>
Helicobacter spp.	3. Metronidazole 4. Tetracycline derivative 1. Metronidazole plus amoxicillin or tetracycline or clarithromycin 2. Amoxicillin and
Hepatic encephalopathy	clarithromycin 3. Clarithromycin 1. Neomycin 2. Ampicillin
Salmonella spp.*	<ol> <li>Metronidazole</li> <li>Quinolones</li> <li>Potentiated sulfas</li> <li>Ampicillin or amoxicillin</li> <li>Aminoglycosides</li> <li>Chloramphenicol</li> </ol>

<sup>\*</sup> Usually administered parenterally for the treatment of bacteremia.

Most infections involving anaerobes usually have coexisting aerobic bacterial infection, which should be considered when selecting antimicrobial agents.

Anaerobic infections are commonly associated with infections of the oropharynx, CNS, subcutaneous space, musculoskeletal system, gastrointestinal tract, liver, and female genital tract, and they are relatively common in animals with aspiration pneumonia or consolidated lung lobes (Fig. 93-1). Dogs and cats with gingivitis or stomatitis, rhinitis, retrobulbar abscesses, retropharyngeal abscesses, aspiration pneumonia, pyothorax, otitis media or interna, CNS infection, bite wounds, open wounds, open fractures, osteomyelitis, peritonitis, bacterial hepatitis, pyometra, vaginitis, bacteremia, and valvular endocarditis should be suspected to be infected with anaerobes. Anaerobic infections also should be considered in animals with a history of fighting, a foreign body, recent surgery, recent dental procedures, a history of immunosuppressive drugs or diseases, infections resistant to aminoglycosides or fluoroquinolones, lesions with a putrid



**TABLE 93-6** 

Empirical Antibiotic Choices for Dogs and Cats with CNS and Musculoskeletal Infections

ORGAN SYSTEM OR INFECTIOUS AGENT	ANTIBIOTIC CHOICES
•	
CNS Encephalitis	1. Chloramphenicol
Lincephallins	Potentiated sulfas
	3. Quinolone
Otitis media/interna	Amoxicillin     Amoxicillin or amoxicillin-
Omis media/imema	clavulanate
	2. Chloramphenicol
	3. Clindamycin
	<ul><li>4. First-generation cephalosporin</li><li>5. Quinolone</li></ul>
Tavamimama ais /	
Toxoplasmosis/ neosporosis	Clindamycin     Patantintad autima
	2. Potentiated sulfas
المعمل مام مام مام	3. Pyrimethamine
Musculoskeletal	1 F:
Discospondylitis	First-generation cephalosporin     Amoxicillin-clavulanate
	3. Clindamycin
	4. Chloramphenicol
Daniel and a second	5. Quinolone
Hepatozoonosis	1. Acute: clindamycin,
	potentiated sulfas, and
	pyrimethamine
O	2. Chronic: decoquinate
Osteomyelitis	Amoxicillin-clavulanate
	2. Clindamycin
	3. First-generation cephalosporin
	4. Chloramphenicol
<b>-</b>	5. Quinolone
Toxoplasmosis/	1. Clindamycin
neosporosis	2. Potentiated sulfas
	<ol><li>Pyrimethamine</li></ol>
Polyarthritis	
Bartonella vinsonii	1. Azithromycin
	2. Quinolone
	3. Azithromycin plus quinolone
Borrelia burgdorferi	Doxycycline (tetracycline
	derivative)
	2. Amoxicillin
Ehrlichia/Anaplasma	<ol> <li>Doxycycline (tetracycline)</li> </ol>
	derivative)
	<ol><li>Chloramphenicol</li></ol>
	3. Imidocarb
L-form bacteria or	<ol> <li>Doxycycline (tetracycline</li> </ol>
Mycoplasma	derivative)
	<ol><li>Chloramphenicol</li></ol>
	3. Quinolone
Rickettsia rickettsii	Doxycycline (tetracycline
	derivative)
	2. Quinolone

CNS, Central nervous system.



**TABLE 93-7** 

Empirical Antibiotic Choices for Dogs and Cats with Urogenital Infections

ORGAN SYSTEM OR INFECTIOUS AGENT	ANTIBIOTIC CHOICES
Aerobic urinary tract	1. Amoxicillin or amoxicillin-
infections	clavulanate
	2. First-generation
	cephalosporin
	3. Potentiated sulfas
	4. Quinolone
Brucella canis	1. Quinolone
	2. Minocycline or doxycycline
	cycled with a quinolone
Leptospira spp.	1. Penicillin G or ampicillin IV
	during acute phase and
	amoxicillin PO during
	chronic phase
	Doxycycline to eliminate
Mastitis	renal carriers
	1. First-generation
	cephalosporin  2. Amoxicillin or amoxicillin-
	clavulanate
Myconlasma	
Mycoplasma/ Ureaplasma	Doxycycline     Chloramphenicol
	3 Quinolone
Prostatitis	Potentiated sulfas
	Quinolone
	3. Chloramphenicol
	4. Erythromycin
	5. Clindamycin
Pyometra	Quinolone and amoxicillin
	2. Chloramphenicol
	3. Potentiated sulfas
	Amoxicillin-clavulanate

IV, Intravenous; PO, oral.

odor or black discharge, a painful lesion with a serosanguineous discharge, neutrophilic inflammation with cytologically evident bacteria but negative aerobic culture, and the presence of "sulfur granules" on cytology. The reader is referred to Chapter 92 for a discussion of the cytologic and cultural characteristics of anaerobic infections. Flaccid paralysis (Clostridium botulinum), rigid paralysis and trismus (Clostridium tetani) and subcutaneous gas production occur in association with some anaerobic infections.

Improving the blood supply and oxygenation of the infected area is the primary goal for treatment of anaerobic infections. Antibiotic therapy should be used concurrently with drainage or debridement. Parenteral antibiotics should be administered for several days in dogs or cats with pyothorax, pneumonia, peritonitis, or clinical signs consistent with bacteremia. Ampicillin, amoxicillin, amoxicillin-clavulanate, clindamycin, metronidazole, cephalosporins (first and second generation), potentiated sulfas, and chloramphenicol are

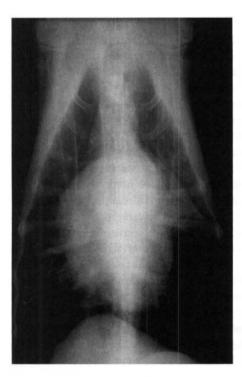


FIG 93-1
Consolidated lung lobe in a dog with aspiration pneumonia and anaerobic involvement.

commonly used for the treatment of anaerobic infections (see Table 93-3). *Bacteroides* spp. are commonly resistant to ampicillin and clindamycin, so if gram-negative coccobacilli are detected cytologically in a neutrophilic exudate—particularly if associated with the oral cavity—metronidazole, a first-generation cephalosporin, or amoxicillin-clavulanate should be administered instead of a penicillin derivative. Because concurrent anaerobic and aerobic infections occur frequently, combination antimicrobial treatment is often indicated, particularly if life-threatening signs of bacteremia exist.

# BACTEREMIA AND BACTERIAL ENDOCARDITIS

Bacteremia can be transient, intermittent, or continuous. Routine dentistry is a common cause of transient bacteremia. Immunosuppressed or critically ill animals commonly develop intermittent bacteremia; the source of infection is commonly the genitourinary or gastrointestinal systems. Continuous bacteremia occurs most frequently in association with bacterial endocarditis. Bacteremic animals have intermittent fever, depression, and clinical signs associated with the primary organ system infected. Sepsis is the systemic response to infection and is manifested by peripheral circulatory failure (septic shock).

Staphylococcus, Streptococcus, Enterococcus, Corynebacterium, Escherichia coli, Salmonella, Klebsiella, Enterobacter, Pseudomonas, Proteus, Pasteurella, Clostridium, Fusobacte-

rium, and Bacteroides organisms are commonly isolated from the blood of bacteremic animals. Bacterial endocarditis is often caused by Staphylococcus aureus, E. coli, or  $\beta$ -hemolytic Streptococcus infection. Bartonella vinsonii (dogs) and B. quintana (cats and dogs; see Chapter 95) have recently been associated with bacterial endocarditis (Sykes et al., 2006).

If the source of bacteremia or bacterial endocarditis is from an area with mixed flora, such as the gastrointestinal tract, or if the animal has life-threatening clinical signs of disease, an antibiotic or combination of antibiotics that is effective against gram-positive, gram-negative, aerobic, and anaerobic organisms should be used (a four-quadrant approach). An aminoglycoside or quinolone for gramnegative organisms combined with ampicillin, a firstgeneration cephalosporin, metronidazole, or clindamycin for gram-positive and anaerobic organisms is a commonly prescribed combination treatment (see Table 93-4). Secondand third-generation cephalosporins, ticarcillin combined with clavulanate, and imipenem are some of the agents with a four-quadrant spectrum. After parenteral treatment with these drugs for 5 to 7 days, oral treatment is selected on the basis of culture and antimicrobial susceptibility results. Optimal treatment for valvular endocarditis from bartonellosis in dogs has not be determined, but the combination of azithromycin and a fluoroquinolone or rifampin may be required in some cases (see Chapter 95). Oral treatment is continued for at least 4 to 6 weeks, particularly in dogs or cats with bacterial endocarditis. The blood culture should be rechecked 1 and 4 weeks after discontinuation of therapy to confirm control of the infection. The prognosis in dogs and cats with bacterial endocarditis is guarded to poor because of damage to the infected heart valves (see Chapter 6).

# CENTRAL NERVOUS SYSTEM INFECTIONS

Chloramphenicol, the sulfonamides, trimethoprim, metronidazole, and the quinolones penetrate the CNS and should be chosen for empirical treatment of suspected bacterial infections of this system (see Table 93-6). Anaerobic bacterial infection and rickettsial infections (*Ehrlichia* spp. and *R. rickettsii*) of the CNS occur in some cases, making chloramphenicol a logical first choice. Multiple other drugs, including penicillin derivatives, tetracyclines (doxycycline), and clindamycin, may cross into the cerebrospinal fluid when inflammation exists. Clindamycin achieves adequate brain tissue concentrations in normal cats for the treatment of toxoplasmosis. Potentiated sulfas are alternative anti-*Toxoplasma* drugs.

# GASTROINTESTINAL TRACT AND HEPATIC INFECTIONS

Oral administration of antibiotics is indicated for the treatment of small intestinal bacterial overgrowth, hepatic

encephalopathy, cholangiohepatitis, hepatic abscessation, and infection by *Helicobacter* spp., *Campylobacter* spp., *Clostridium perfringens, Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., *Tritrichomonas foetus*, and *Toxoplasma gondii* (see Table 93-5). Administration of parenteral antibiotics is indicated in dogs and cats with bacteremia from translocation of enteric flora or *Salmonella* infection.

Giardia spp. infections often respond clinically to the administration of metronidazole, but infection is usually not eliminated. Administration of metronidazole benzoate at 25 mg/kg q12h PO for 7 days was effective in suppressing cyst shedding to below detectable limits in 26 cats (Scorza et al., 2004). This is the maximal dose of metronidazole that should be used; CNS toxicity can be induced by overdosing or as a cumulative neurotoxin. Fenbendazole is the most commonly used alternate drug. Metronidazole also has the advantage of helping correct secondary small intestinal bacterial overgrowth. For T. foetus infections, ronidazole at 30 mg/kg PO q12h for 14 days eliminated clinical signs of disease and trophozoites from cats infected with one strain of the organism. In the United States this drug currently must be purchased from a custom pharmacy. CNS toxicity is also common with ronidazole.

Sequential administration of clindamycin followed by tylosin blocked oocyst shedding and resolved diarrhea in one cat with chronic clinical cryptosporidiosis. Tylosin (10-15 mg/kg q12h PO) has apparently been successful in lessening diarrhea and oocyst shedding in multiple other cats and dogs with diarrhea that were positive for Cryptosporidium. However, infection is not eliminated. Unfortunately, tylosin is quite bitter and usually has to be given to cats in capsules. Treatment duration may need to be weeks. Paromomycin can be effective for lessening diarrhea and oocyst shedding associated with cryptosporidiosis in cats and also is an alternate anti-Giardia drug. However, this orally administered aminoglycoside may cross the diseased intestinal wall and result in renal toxicity and should never be used in cats with bloody diarrhea. In cats with naturally occurring cryptosporidiosis, response to azithromycin has been variable (Lappin MR, unpublished data, 2005). If tried, use 10 mg/kg PO weekly for at least 10 days. If responding, continue treatment for at least 1 week past clinical resolution. The Toxoplasma gondii oocyst shedding period can be shortened by administration of clindamycin or sulfadimethoxine. Cystoisospora spp. generally respond to the administration of sulfadimethoxine or other sulfa-containing drugs.

Clostridium perfringens and bacterial overgrowth generally respond to treatment with tylosin, metronidazole, ampicillin, amoxicillin, or tetracyclines. The drug of choice for campylobacteriosis is erythromycin; however, oral administration of quinolones or chloramphenicol are often less likely to potentiate vomiting. Salmonellosis should only be treated parenterally because of rapid resistance that occurs after oral administration of antibiotics. Appropriate antibiotics for the empirical treatment of salmonellosis while awaiting susceptibility testing results include ampicillin and trimethoprim-sulfa; quinolones are also effective. Helico-

bacter spp. infections are usually treated with the combination of metronidazole and tetracycline or amoxicillin and clarithromycin. In cats the use of clarithromycin alone may be logical because the species is often difficult to treat with multiple drugs.

Dogs or cats with apparent bacteremia from enteric bacteria should be treated with parenteral antibiotics with a spectrum against anaerobic and gram-negative organisms. The combination of enrofloxacin with a penicillin or first-generation cephalosporin is generally effective. Intravenous metronidazole can also be used. Second-generation cephalosporins or imipenem is also an appropriate choice.

The most common bacteria in one study of hepatic infections were *E. coli, Enterococcus, Streptococcus, Clostridium*, and *Bacteroides* (Wagner et al., 2007). Dogs or cats with hepatic infections and signs of bacteremia should be treated with antibiotics that kill gram-positive, gram-negative, and anaerobic bacteria, as previously discussed. Nonbacteremic hepatic infections generally respond to amoxicillinclavulanate, first-generation cephalosporins, or metronidazole; a fluoroquinolone should be added if signs of sepsis are present. Decreasing numbers of enteric flora by oral administration of penicillins, metronidazole, or neomycin can lessen the clinical signs of hepatic encephalopathy.

## MUSCULOSKELETAL INFECTIONS

Osteomyelitis and discospondylitis are commonly associated with infections by *Staphylococcus*, *Streptococcus*, *Proteus*, *Pseudomonas* spp., *E. coli*, and anaerobes. First-generation cephalosporins, amoxicillin-clavulanate, and clindamycin are logical antibiotics for empirical therapy of these conditions because of their spectrum of activity against the grampositive organisms and anaerobic bacteria and their ability to achieve high concentrations in bone (see Table 93-6). Quinolones should be used if gram-negative organisms are suspected. Antibiotic treatment should be continued for a minimum of 2 weeks beyond resolution of radiographic changes.

Dogs and cats with septic polyarthritis should be treated in the same way as those with osteomyelitis. The source of infection should be removed if possible. Bartonella vinsonii, Ehrlichia spp., Rickettsia rickettsii, Borrelia burgdorferi, Mycoplasma organisms, and L-form bacteria can induce nonseptic, suppurative polyarthritis. Occasionally, morulae of Ehrlichia spp. are identified cytologically in the joint fluid. In general, the cytologic findings in joint fluid induced by these agents are similar to those of immune-mediated polyarthritis. For this reason doxycycline is a logical empirical antibiotic choice for dogs with nonseptic, suppurative polyarthritis pending the results of further diagnostic tests. Amoxicillin is an alternative drug for the treatment of B. burgdorferi infection. Fluoroquinolones can also be used for R. rickettsii, Mycoplasma, and l-form bacteria infections. B. vinsonii infection may require the administration of azithromycin, with or without concurrent fluoroquinolones.

Muscle disease from T. gondii infection often resolves during treatment with clindamycin hydrochloride. Although many dogs with neosporosis die, some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine; sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine; or clindamycin alone. For treatment of acute Hepatozoon americanum infection, the combination of trimethoprim-sulfadiazine, pyrimethamine, and clindamycin for 14 days is highly successful; the use of decoquinate at 10 to 20 mg/kg q12h with food lessens the likelihood of recurrence of clinical disease and prolongs survival

# RESPIRATORY TRACT INFECTIONS

Most bacterial upper respiratory infections are secondary to other primary diseases, including foreign bodies, viral infections, tooth root abscesses, neoplasms, trauma, and fungal infections. After the epithelium of the nose and sinuses is inflamed, normal bacterial flora can colonize and perpetuate inflammation; deep infection can result in chondritis and osteomyelitis. Because the upper respiratory passageways have a normal flora, it is difficult to assess the results of culture and antimicrobial susceptibility testing in these tissues. The source of the primary insult should always be removed if possible. Broad-spectrum antibiotics with an anaerobic spectrum, including amoxicillin, amoxicillinclavulanate, potentiated sulfas, and first-generation cephalosporins, are commonly prescribed empirically to treat upper respiratory infections caused by normal flora overgrowth (see Table 93-4). Treatment duration is generally 1 to 2 weeks for acute, first-time infections. Dogs and cats with chronic rhinitis and suspected osteochondritis that respond to antibiotics should be treated for a minimum of 4 to 6 weeks or until clinical signs have been resolved for 2 weeks. Chronic rhinitis often responds to treatment with clindamycin because of the excellent anaerobic and gram-positive spectrum and its ability to penetrate cartilage and bone well. Bordetella bronchiseptica, Mycoplasma spp., and Chlamydophila felis infection of cats are primary bacterial pathogens that infect the upper respiratory tissues. If the animal responds poorly to broad-spectrum antibiotics, doxycycline, azithromycin, chloramphenicol, or quinolones can be administered; Chlamydophila, Bordetella, and Mycoplasma organisms generally respond to these drugs. Epistaxis can be caused by B. vinsonii, E. canis, and R. rickettsii. No evidence currently supports Bartonella spp. as a cause of rhinitis in cats. Canine bartonellosis often fails to respond to the administration of doxycycline but can be successfully treated with azithromycin. Canine kennel cough syndrome caused by Bordetella or Mycoplasma spp. is usually effectively treated with doxycycline, chloramphenicol, quinolones, or amoxicillinclavulanate. Bacterial bronchitis in cats generally responds to administration of amoxicillin-clavulanate. In dogs and cats with chronic bronchitis, doxycycline, chloramphenicol, quinolones, or amoxicillin-clavulanate are rational empirical antibiotic choices.

Common bacteria associated with pneumonia in dogs include E. coli, Klebsiella spp., Pasteurella spp., Pseudomonas spp., B. bronchiseptica, Streptococcus spp., Staphylococcus spp., and Mycoplasma spp. In cats, Bordetella, Pasteurella, and Mycoplasma organisms are commonly isolated. Aspiration of gastrointestinal contents is a common cause of bacterial pneumonia with a mixed population of bacteria. Multiple species of bacteria are typically cultured from dogs and cats with bronchopneumonia. B. bronchiseptica is the most important primary pathogen in dogs and cats; most other bacteria colonize after airways have been previously damaged. If consolidated lung lobes are detected radiographically, an anaerobic infection should be assumed. Whether species of Mycoplasma infecting dogs and cats are capable of being primary respiratory pathogens is unknown. Chlamydophila infection in cats is not a common cause of lower respiratory tract infection. Yersinia pestis causes pneumonia in cats in western states (see Chapter 100); aminoglycosides, tetracycline derivatives, and quinolones can be used successfully.

In dogs and cats with bacterial pneumonia, culture and antimicrobial susceptibility testing should be performed on secretions collected by transtracheal wash or bronchoalveolar lavage. If the animal shows signs of bacteremia or if radiographic evidence of consolidated lung lobes is present, parenteral administration of a four-quadrant antibiotic choice, as previously discussed for bacteremia, should be used initially. Quinolones combined with clindamycin or azithromycin or chloramphenicol alone is a good choice for animals with consolidated lung lobes because of their broad spectrum, excellent tissue penetration, and efficacy against B. bronchiseptica (see Table 93-5). In animals with pneumonia but without clinical signs of bacteremia or consolidated lung lobes, broad-spectrum antibiotics, including amoxicillin, amoxicillin-clavulanate, potentiated sulfas, and firstgeneration cephalosporins, may be effective. Surface-dwelling organisms such as B. bronchiseptica and Mycoplasma may respond to nebulization of gentamicin diluted in sterile saline (25 to 50 mg in 3 to 5 mL saline/nebulization). Treatment for bacterial pneumonia should be continued for at least 4 weeks or for 1 to 2 weeks beyond resolution of clinical and radiographic signs of disease.

T. gondii occasionally causes pneumonia in neonatally infected, transplacentally infected, and immunosuppressed cats and dogs (see Chapter 99). Clindamycin or potentiated sulfas should be used if toxoplasmosis is suspected. Azithromycin may also be effective for the treatment of toxoplasmosis. Neospora caninum has occasionally been associated with pneumonia in dogs and should be treated with a combination of clindamycin and potentiated sulfas.

If pyothorax is attributable to penetration of foreign material from an airway or esophagus into the pleural space, thoracotomy is usually required for removal of devitalized tissue and the foreign body (see Chapter 23). Pyothorax occasionally results from hematogenous spread of bacteria to the pleural space; this may be common in cats. Pleural lavage through chest tubes is the most effective treatment for patients with pyothorax and no obvious foreign material. Most dogs and cats with pyothorax have mixed aerobic and anaerobic bacterial infections. Animals with pyothorax and clinical signs of bacteremia should initially receive parenteral four-quadrant antibiotics, as previously discussed for bacteremia.

# SKIN AND SOFT TISSUE INFECTIONS

Staphylococcus pseudointermedius is the most common cause of pyoderma in dogs and cats. Deep pyoderma can be induced by any organism, including gram-negative types. Most soft tissue infections, including open wounds and abscesses, are infected with a mixed population of bacteria; the aerobic and anaerobic flora from the mouth are often involved. Recommended empirical antibiotic choices for routine cases of pyoderma and soft tissue infections are listed in Table 93-3. Antibiotics with a broad spectrum, such as first-generation cephalosporins and amoxicillin-clavulanate, are often first choices. Other β-lactamase-resistant penicillins, such as oxacillin, dicloxacillin, and cloxacillin, also can be used. Potentiated sulfas can be used to treat dogs and cats with superficial pyoderma but should be avoided if longterm treatment is needed because bacterial resistance occurs quickly. Cutaneous and soft tissue infections that do not respond to these antibiotics may be caused by gram-negative bacteria, L-form bacteria, Mycoplasma organisms, rapidly growing Mycobacterium spp., systemic fungi, or Sporothrix schenckii. Quinolones are the antibiotic class of choice for the treatment of gram-negative infections. Animals that do not respond to empirical antibiotic treatment should undergo further diagnostic testing or be treated with antibiotics known to have an effect against the less-common pathogens (see Table 93-3). If not previously done, microscopic examination of tissue or pustule aspirates should be performed for the presence of Sporothrix organisms and bacteria morphologically similar to Mycobacterium spp. After surgical preparation of the skin, deep tissues should be obtained for aerobic, anaerobic, Mycoplasma, fungal, and atypical Mycobacterium spp. culture (see Chapter 92).

#### UROGENITAL TRACT INFECTIONS

Microscopic examination and Gram stain of urine sediment aids in the empirical choice of an antibiotic in dogs and cats with signs of urinary tract infection. Culture and antimicrobial susceptibility testing should always be performed if possible. Approximately 75% of urinary tract infections in dogs are caused by gram-negative organisms; *E. coli, Proteus, Klebsiella, Pseudomonas,* and *Enterobacter* infections are common. In cats that have been previously catheterized, *E. coli* is most common; *Staphylococcus* and *Streptococcus* organisms are common after urethrostomy (see Chapter 45).

In bitches with simple, first-time urinary tract infections, amoxicillin or amoxicillin-clavulanate should be used if cocci are observed; potentiated sulfas or first-generation cephalosporins should be used if rods are observed. Quinolones should be reserved for life-threatening or resistant infections. Many antibiotics do not penetrate the prostate unless it is markedly inflamed. Because the prostate can be a source of recurrent urinary tract infection, all male dogs with urinary tract infection should be assumed to have prostatitis, and antibiotics that penetrate the prostate should be chosen (see Table 93-7). The majority of urinary tract infections in cats respond to amoxicillin. Administration of antibiotics for 10 to 14 days is generally sufficient for simple urinary tract infections. Urinalysis, culture, and antimicrobial susceptibility testing should be performed 7 days after finishing treatment if possible.

Mycoplasma and Ureaplasma infections have been documented in dogs with clinical signs of urinary tract infections. If poor response to penicillin derivatives, cephalosporins, or potentiated sulfas is observed, further diagnostics should be performed. If empirical therapy is deemed necessary, chloramphenicol, doxycycline, or quinolone treatment can be administered and may be more effective for Mycoplasma and Ureaplasma organisms.

All dogs and cats with urinary tract infection and azotemia should be assumed to have pyelonephritis and be treated accordingly, even if further diagnostic procedures are not performed. Treatment for pyelonephritis should be based on susceptibility results if possible; potentiated sulfa combinations or quinolones are good empirical choices. If Leptospira spp. infection is suspected, intravenous administration of ampicillin is indicated (see Chapter 95). If renal insufficiency exists, the tetracyclines (except doxycycline) and aminoglycosides should be avoided, and the dosage or dosing interval of quinolones and cephalosporins should be extended proportionally to the diminution in renal function. The new dosage can be calculated by multiplying the current dosage by the result obtained when the mean normal creatinine concentration is divided by the patient's creatinine concentration. The new dosing interval can be calculated by multiplying the current dosing interval by the result obtained when the patient's creatinine concentration is divided by the mean normal creatinine concentration. Treatment for pyelonephritis and other chronic, complicated urinary tract infections should be continued for at least 6 weeks. Urinalysis, culture, and antimicrobial susceptibility testing should be performed 7 and 28 days after treatment. Some infections cannot be eliminated and require administration of pulse antibiotic therapy.

Most bacterial prostatic infections involve gram-negative bacteria. During acute prostatitis almost all antibiotics penetrate the prostate well because of inflammation. After reestablishment of the blood-prostate barrier in dogs with chronic prostatitis, the acidic prostatic fluid allows only the basic antibiotics (pK<sub>a</sub> less than 7) to penetrate well (see Table 93-7). Chloramphenicol, because of its high lipid solubility, also penetrates prostatic tissue well. In acute prostatitis

administration of acidic antibiotics, including penicillins and first-generation cephalosporins, may initially penetrate well, lessening clinical signs of disease but not eliminating the infection. This predisposes to chronic bacterial prostatitis and prostatic abscessation. For this reason the use of penicillins and first-generation cephalosporins is contraindicated for the treatment of urinary tract infections in male dogs. In dogs with chronic prostatitis antimicrobial therapy should be continued for at least 6 weeks. Urine and prostatic fluid should be cultured 7 days and 28 days after therapy.

Brucella canis causes a number of clinical syndromes in dogs, including epididymitis, orchitis, endometritis, still-births, abortion, discospondylitis, and uveitis. Ovariohyster-ectomy or neutering lessens contamination of the human environment. (See Chapter 100 for a discussion of the zoonotic potential.) Long-term antibiotic administration usually does not lead to a complete cure (Wanke et al., 2006). Some dogs become antibody-negative, but the organism can still be cultured from tissues. Several antibiotic protocols have been suggested for dogs with brucellosis (see Table 93-7). However, owners should be carefully counseled concerning zoonotic risks before initiating treatment.

Vaginitis generally results from overgrowth of normal flora secondary to primary diseases, including herpesvirus infection, urinary tract infection, foreign bodies, vulvar or vaginal anomalies, vaginal or vulvar masses, or urinary incontinence. In dogs and cats with bacterial vaginitis from overgrowth of flora and resolution of the primary insult, broad-spectrum antibiotics, including amoxicillin, potentiated sulfas, first-generation cephalosporins, tetracycline derivatives, and chloramphenicol, are typically successful. Because *Mycoplasma* and *Ureaplasma* organisms are part of the normal vaginal flora, providing a clinical disease association is virtually impossible; positive cultures do not confirm disease because of the organism (see Chapter 95). Hence a positive vaginal culture from an asymptomatic dog (excluding *B. canis*) is meaningless.

In all dogs and cats with pyometra, ovariohysterectomy or medically induced drainage of the uterus is imperative. Antibiotic treatment is for the bacteremia that commonly occurs concurrently (i.e., *E. coli* and anaerobes). Animals with clinical signs of bacteremia or sepsis should be treated with a four-quadrant antibiotic choice (see Table 93-5). Broad-spectrum antibiotics with efficacy against *E. coli*, such as potentiated sulfas or amoxicillin-clavulanate, are appropriate empirical choices pending the results of culture and antimicrobial susceptibility testing. Potentiated sulfas and the quinolones commonly are effective for *E. coli* but are not

as effective as other drugs for the treatment of anaerobic infections in vivo,

Ampicillin, amoxicillin, and first-generation cephalosporins achieve good concentrations in milk and are relatively safe for the neonate; therefore they can be used in the empirical treatment of mastitis. Chloramphenicol, quinolones, and tetracycline derivatives should be avoided because of potential adverse effects on the neonate.

# Suggested Readings

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# CHAPTER Prevention of Infectious Diseases

# CHAPTER OUTLINE

BIOSECURITY PROCEDURES FOR SMALL ANIMAL HOSPITALS

General Biosecurity Guidelines
Patient Evaluation
Hospitalized Patients
Basic Disinfection Protocols
BIOSECURITY PROCEDURES FOR CLIENTS
VACCINATION PROTOCOLS

Vaccine Types Vaccine Selection Vaccination Protocols for Cats Vaccination Protocols for Dogs

Preventing infections is always preferred over treating infections. Avoiding exposure is the most effective way to prevent infections. Most infectious agents of dogs and cats are transmitted in fecal material, respiratory secretions, reproductive tract secretions, or urine; by bites or scratches; or by contact with vectors or reservoirs. Some infectious agents such as FHV-1, Bordetella bronchiseptica, and canine influenza virus can be transmitted by direct contact with clinically normal, infected animals. Many infectious agents are environmentally resistant and can be transmitted by contact with a contaminated environment (fomites). The avoidance of zoonotic transfer of infectious agents is extremely important because some zoonotic diseases, such as plague and rabies, are life threatening (see Chapter 100). Recognition of risk factors associated with infectious agents is the initial step in the prevention of infectious diseases. Veterinarians should strive to understand the biology of each infectious agent so they can counsel clients and staff on the best strategies for prevention.

Vaccines available for some infectious agents can prevent infection or lessen clinical illness when infection occurs. However, vaccines are not uniformly effective, are not available for all pathogens, and sometimes induce serious adverse effects. Therefore the development of sound biosecurity procedures is paramount to avoid exposure to infectious agents when developing a preventive medicine program.

# BIOSECURITY PROCEDURES FOR SMALL ANIMAL HOSPITALS

Most hospital-borne infections (nosocomial) can be prevented by following simple biosecurity guidelines (Box 94-1). The following are some general guidelines to consider that were adapted from those used at the Veterinary Medical Center at Colorado State University (http://csuvets.colostate.edu/biosecurity).

#### **GENERAL BIOSECURITY GUIDELINES**

Contaminated hands are the most common source of infectious agent transmission in the hospital environment. Fingernails of personnel having patient contact should be cut short. Hands should be washed before and after attending to each individual animal as follows. Collect clean paper towels and use to turn on water faucets, wash hands for 30 seconds with antiseptic soap being sure to clean under fingernails, rinse hands thoroughly, use the paper towel to dry hands, and use the paper towel to turn off the water faucets. Use of antiseptic lotion should be encouraged. Personnel should not touch patients, clients, food, doorknobs, drawer or cabinet handles or contents, equipment, or medical records with soiled hands or gloves.

All employees should wear an outer garment, such as a smock or scrub suit, when attending to patients. Footwear should be protective, clean, and cleanable. A minimum of two sets of outer garments should always be available, and they should be changed immediately after contamination with feces, secretions, or exudates. Equipment such as stethoscopes, pen lights, thermometers, bandage scissors, lead ropes, percussion hammers, and clipper blades can be fomites and should be cleaned and disinfected after each use with animals likely to have a transmissible infectious disease. Disposable thermometer covers or thermometers should be used.



BOX 94-1

#### General Hospital Biosecurity Guidelines

- Wash hands before and after each patient contact.
- Wear gloves when handling patients when zoonotic diseases are on the list of differential diagnoses.
- Minimize contact with hospital materials (instruments, records, door handles, etc.) while hands or gloves are contaminated.
- Always wear an outer garment, such as a smock or scrub shirt, when handling patients.
- Change outer garments when soiled by feces, secretions, or exudates.
- Clean and disinfect equipment (stethoscopes, thermometers, bandage scissors, etc.) after each use with animals likely to have an infectious disease.
- Examination tables, cages, and runs should be cleaned and disinfected after each use.
- Litter boxes and dishes should be cleaned and disinfected after each use.
- · Place animals with suspected infectious diseases into an examination room or an isolation area immediately on admission into the hospital.
- Treat animals with suspected infectious diseases as outpatients if possible.
- Procedures that use general hospital facilities, such as surgery and radiology, should be postponed until the end of the day if possible.
- Do not consume fluids or drink in areas where patient care is provided.

To avoid zoonotic transfer of infectious diseases, food or drink should not be consumed in areas where animal care is provided. All areas where animals are examined or treated should be cleaned and disinfected immediately after use, irrespective of infectious disease status of the individual animal.

#### PATIENT EVALUATION

Prevention of infectious diseases starts with the front desk personnel. Staff should be trained to recognize the presenting complaints for the infectious agents in the geographic area of the hospital. Animals with gastrointestinal or respiratory diseases are the most likely to be contagious. Infectious gastrointestinal disease should be suspected in all dogs and cats with small- or large-bowel diarrhea whether the syndrome is acute or chronic. Infectious respiratory disease should be suspected in all dogs and cats with sneezing (especially those with purulent oculonasal discharge) or coughing (especially if productive). The index of suspicion for infectious diseases is increased for dogs or cats with acute disease and fever, particularly if the animal is from a crowded environment such as a breeding facility, boarding facility, or shelter.

Front desk personnel should indicate clearly on the hospital record that gastrointestinal or respiratory disease is present. If the presenting complaint is known before admission into the hospital, an optimal method would be to meet the client in the parking area to determine the infectious disease risk before the pet enters the hospital. If an infectious gastrointestinal or respiratory disease is suspected, the animal should be transported (i.e., not allowed to walk on the premises) to an examination room or the isolation facility. If a patient with acute gastrointestinal or respiratory disease is presented directly to the reception desk, the receptionist should contact the receiving clinician, technician, or student immediately and coordinate placement of the animal in an examination room to minimize hospital contamination. Animals with suspected infectious diseases should be treated as outpatients if possible. If hospitalization is required, the animal should be transported to the appropriate housing area by the shortest route possible, preferably with a gurney to lessen hospital contamination. The gurney and any hospital materials in contact with potentially contaminated employees (including examination tables and doorknobs) should be immediately cleaned and disinfected as previously mentioned.

#### HOSPITALIZED PATIENTS

If possible, all animals with suspected infectious diseases, such as Salmonella spp., Campylobacter spp., parvovirus infection, kennel cough syndrome, acute feline upper respiratory disease syndrome, rabies, or plague, should be housed in an isolated area of the hospital. The number of staff members entering the isolation area should be kept to a minimum. On entry into the isolation area, outerwear should be left outside and surgical booties or other disposable shoe covers should be placed over the shoes. Alternatively, a foot bath filled with disinfectant should be placed by the exit and used when leaving the area. The room should be entered and a disposable gown (or smock designated for the patient) and latex gloves should be put on. A surgical mask should be worn when attending cats with plague, and extreme care should be taken to avoid being bitten. Separate equipment and disinfectant supplies should be used in the isolation

All biologic materials submitted to clinical pathology laboratories or diagnostic laboratories from animals with suspected or proven infectious diseases should be clearly marked as such. Fecal material should be placed in a plastic, screw-capped cup with a tongue depressor or while the clinician is wearing gloves. Place the cup in a clean area and place the lid on with a clean, gloved hand. Remove the used gloves and place the cup in a second bag clearly marked with the name of the infectious disease suspected. The outer surface of the bag should be disinfected before leaving the isolation

Disposable materials should be placed in plastic bags in the isolation area. The external surfaces of the bags should be sprayed with a disinfectant before being removed from the isolation area. After attending to the patient, contaminated equipment and surfaces should be cleaned and disinfected, and contaminated outer garments and shoe covers

should be removed. Hands should be washed after discarding the contaminated outerwear. Dishes and litter pans should be cleansed thoroughly with detergent before returning them to the central supply area of the hospital. Optimally, materials such as outerwear and equipment to be returned to the central supply area should be placed in plastic bags and sprayed with a disinfectant before transport. Procedures requiring general hospital facilities such as surgery and radiology should be postponed to the end of the day, if possible, and the contaminated areas disinfected before use with other animals. Animals should be discharged by the shortest path to the parking lot possible.

Some animals with infectious diseases can be maintained in the general hospital boarding or treatment areas with special management techniques. For example, cats positive for the feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) should not be placed in the isolation area, if possible, to avoid exposing them to other infectious agents. Because neither of these two viruses is transmitted by aerosolization, cats with these infectious diseases can be housed in close proximity to other cats. The cages should be labeled appropriately, and the infected cats should not be caged next to or above seronegative cats. In addition, no direct contact or sharing of litter boxes or food bowls should occur between infected and naïve cats.

#### **BASIC DISINFECTION PROTOCOLS**

To lessen the spread of potential infectious agents, hospitalized animals should never be moved from cage to cage. The key to effective disinfection is cleanliness. Cage papers and litter boxes soiled by feces, urine, blood, exudates, or respiratory secretions should be removed and placed in trash receptacles. Bulk fecal material should also be placed in trash receptacles.

Many infectious agents are resistant to disinfectants or require prolonged contact time to be inactivated (Greene, 2006). Contaminated surfaces, including the cage or run floors, walls, ceiling, door, and door latch, should be wetted thoroughly with a disinfectant that is then blotted with clean paper towels or mops. Surfaces should be in contact with the disinfectant for 10 to 15 minutes if possible, particularly if known infectious agents are present. Soiled paper towels should be placed in trash receptacles. If infectious disease is suspected, the trash bags should be sealed, the surface of the bag sprayed with a disinfectant, and the trash bags discarded.

Contaminated surfaces in examination rooms should be cleaned to remove hair, blood, feces, and exudates. Examination tables, countertops, floors, canister lids, and water taps should be saturated with disinfectant for 10 minutes. Surfaces should be blotted with paper towels until dry, and the soiled towels should be placed in a trash receptacle. Urine or feces on the floor should be contained with paper towels, blotted, and placed in trash receptacles. The soiled area of the floor should be mopped with disinfectant.

Disinfectants are relatively effective for viral and bacterial agents but require high concentrations and long contact

times to kill parasite eggs, cysts, and oocysts. Cleanliness is the key to lessening hospital-borne infection with these agents; detergent or steam cleaning inactivates most of these agents. Litter pans and dishes should be thoroughly cleaned with detergent and scalding water.

# BIOSECURITY PROCEDURES FOR CLIENTS

Housing animals indoors in a human environment to prevent exposure to other animals, fomites, or vectors is the optimal way to prevent infectious diseases. Some infectious agents can be carried into the home environment with the owners, by vectors, or by paratenic or transfer hosts. Although most infections occur in both immunocompromised and immunocompetent animals, clinical disease is often more severe in immunocompromised animals. Puppies, kittens, old animals, debilitated animals, animals with immunosuppressive diseases (e.g., hyperadrenocorticism, diabetes mellitus, cancer), animals with concurrent infections, and animals treated with glucocorticoids or cytotoxic agents are examples of immunocompromised patients. Avoiding exposure to infectious agents in this group is particularly important because of the potential for increased susceptibility to disease. These animals may also be less likely to have appropriate responses to immunization. Kennels, veterinary hospitals, dog and cat shows, and shelters have an increased likelihood for infectious agent contact because of the concentration of potentially infected animals and should be avoided when possible. Areas such as parks are common sources of infectious agents that survive for long periods in the environment; parvoviruses and enteric parasites are classic examples. Owners should avoid bringing new animals with unknown histories into a home environment with other pets until the new animal is evaluated by a veterinarian for infectious disease risk. If people are in contact with animals outside the home environment, they should wash their hands before contact with their own pet. The owner should consult the veterinarian concerning vaccination protocols and other preventive medical procedures (e.g., routine deworming, flea control, tick control) most indicated for each individual patient.

#### **VACCINATION PROTOCOLS**

#### **VACCINE TYPES**

Vaccines are available for some infectious agents of dogs and cats and can be administered to prevent infection or limit disease. Vaccination stimulates humoral, mucosal, or cell-mediated immune responses. Humoral immune responses are characterized by the production of immunoglobulin M (IgM), IgG, IgA, and IgE class antibodies, which are produced by B-lymphocytes and plasma cells after being presented an antigen by macrophages. Binding of antibodies to an infectious agent or its toxins helps prevent infection or disease by facilitating agglutination (viruses), improving

phagocytosis (opsonization), neutralizing toxins, blocking attachment to cell surfaces, initiating the complement cascade, and inducing antibody-dependent cell-mediated cytotoxicity. Antibody responses are most effective in controlling infectious agents during extracellular replication or toxin production. Cell-mediated immune responses are mediated principally by T-lymphocytes. Antigen-specific T-lymphocytes either destroy the infectious agent or mediate destruction of the agent by producing cytokines that stimulate other white blood cells, including macrophages, neutrophils, and natural killer cells. Cell-mediated immunity is required for the control of most cell-associated infections.

Currently available vaccines are either infectious (attenuated [modified-live] organisms or live virus—vectored recombinant vaccines) or noninfectious (killed virus, killed bacteria [bacterins], and subunit vaccines).

Attenuated vaccines replicate in the host to effectively stimulate an immune response and therefore generally have low antigen mass and do not require adjuvants. Different products are administered locally (e.g., modified-live Bordetella bronchiseptica intranasal vaccine) or parenterally (e.g., modified-live canine distemper vaccine). In live virusvectored recombinant vaccines, the specific DNA that codes for the immunogenic components of the infectious agent is inserted into the genome of a nonpathogenic organism (vector) that will replicate in the species being vaccinated. As the vector replicates in the host, it expresses the immunogenic components of the infectious agent, resulting in the induction of specific immune responses. Because the virusvectored vaccine is live and replicates in the host, adjuvants and high-antigen mass are not required. Because only DNA from the infectious agent is incorporated into the vaccine, no risk of reverting to the virulent parent strain exists, as occasionally occurs with attenuated vaccines. Only vectors that do not induce disease in the animal being vaccinated are used. Another advantage to vaccines of this type is the potential ability to overcome inactivation by maternal antibodies.

Killed virus, killed bacteria (bacterins), and subunit vaccines are noninfectious and therefore usually require higher antigen mass than infectious vaccines to stimulate immune responses because they do not replicate in the host. Some noninfectious vaccines may stimulate immune responses of lesser magnitude and shorter duration than infectious vaccines unless adjuvants are added. Adjuvants improve immune responses by stimulating uptake of antigens by macrophages that present the antigens to lymphocytes. Although adjuvants have historically been associated with vaccine adverse effects, newer generation adjuvants induce less inflammation. Subunit vaccines can be superior to killed vaccines that use the entire organism because only the immunogenic parts of the organism are used, which may decrease the potential for vaccine reactions. However, for some infections use of only one antigen does not adequate induce adequate protection. Native DNA vaccines and genedeleted vaccines are currently being evaluated for several infectious diseases.

#### VACCINE SELECTION

Selection of optimal vaccines for use in dogs and cats is complicated. Multiple products for most infectious agents are available, but efficacy studies that directly compare different products are generally lacking. The veterinarian may need to choose from infectious and noninfectious options for the same vaccine antigen. Some vaccine antigens are for intranasal administration and others are for parenteral administration. Not all vaccines for a given infectious disease are comparable in every situation. Long-term duration of immunity studies and studies evaluating a vaccine's ability to block infection by multiple field strains are not available for all individual products. When making decisions about which products to use or when evaluating a new vaccine, the practitioner should request information concerning efficacy, challenge studies, duration of immunity studies, adverse reactions, and cross-protection capability. Vaccine issues are commonly debated in veterinary journals and continuing education meetings; these are excellent sources of current information.

Not all dogs and cats need all available vaccines. Vaccines are not innocuous and should only be given if indicated. The type of vaccine and route of administration for the disease in question should also be considered. A benefit, risk, and cost assessment should be discussed with the owner of each individual animal before determining the optimal vaccination protocol. For example, FeLV only lives outside the host for minutes; it is highly unlikely that an owner would bring the virus into the household. Therefore cats housed indoors are not likely to come in contact with the virus.

Before administering vaccines, the animal should be evaluated for factors that may influence the ability to respond to the vaccine (Box 94-2) or that may affect whether vaccina-



BOX 94-2

#### Potential Causes of Vaccine Failure

- Protective immune responses were not stimulated by the antigens in the vaccine (humoral versus cell mediated).
- The animal was exposed to a field strain of the organism the vaccine fails to protect against.
- The vaccine-induced immune response waned by the time of exposure.
- The vaccine induced immune response was overwhelmed by the degree of exposure.
- The vaccine was handled or administered improperly.
- The animal was incubating the disease when vaccinated.
- The animal was unable to respond to the vaccine because of immunosuppression.
- The animal was unable to respond to the vaccine because of hypothermia or fever.
- The animal had maternal antibodies that lessened the response to vaccination.
- The modified-live product induced disease.

tion could be detrimental. Hypothermic animals have poor T-lymphocyte and macrophage function and are unlikely to respond appropriately to vaccination. Dogs with body temperature above 39.7° C respond poorly to canine distemper virus vaccines; this may be true for other vaccines as well. Immunosuppressed animals, including those with FeLV infection, FIV infection, canine parvovirus infection, Ehrlichia canis infection, and debilitating diseases, may not respond appropriately to vaccination; modified-live vaccines occasionally induce the disease in these animals.

If high levels of specific antibodies are present, vaccine efficacy is diminished. This is a particularly important consideration when vaccinating puppies or kittens from well-vaccinated dams. Disease may also develop in vaccinated puppies and kittens because infection had already occurred and was incubating when the animal was vaccinated. Vaccines can be rendered ineffective from mishandling. Vaccines should not be administered while the animal is under anesthesia because efficacy can be diminished; if a vaccine reaction occurs, it may be masked by the anesthesia.

Adverse reactions can potentially occur with any vaccine. However, they are relatively uncommon in dogs and cats. In a recent study of more than 1.2 million dogs, the overall rate of adverse reactions was 38.2/10,000 dogs that had received vaccines within the previous 3 days (Moore et al., 2005). In a recent study of 496,189 cats, the overall rate of adverse reactions was 51.6/10,000 cats that had received vaccines within the previous 30 days (Moore et al., 2007). Vaccination has been associated with soft tissue sarcomas in some cats and can be life threatening. These tumors can occur after administration of infectious or noninfectious vaccines. Intranasal products can result in transient sneezing and coughing. Feline vaccines for which the viruses were grown on Crandall Rees feline kidney cell cultures induce antibodies that cross-react with feline renal tissues (Lappin et al., 2005), and some hypersensitized cats have developed lymphocytic-plasmacytic interstitial nephritis (Lappin et al., 2006b). Whether this results in renal disease is currently unknown. Suspected adverse reactions to vaccination should be reported (Paul et al., 2006). Administration of any vaccine to animals with proven vaccine-associated sarcoma or immune-mediated diseases, such as immune-mediated polyarthritis, immune-mediated hemolytic anemia, immunemediated thrombocytopenia, glomerulonephritis, polyradiculoneuritis, is questionable because immune stimulation may exacerbate these conditions.

For some infectious agents, including canine distemper virus, canine parvovirus, feline panleukopenia virus (FPV), feline calicivirus (FCV), and FHV-1, serologic test results have been shown to correlate to resistance to disease on challenge in some studies. The advantages and disadvantages of the use of serologic testing were recently reviewed (Moore et al., 2006). If validated laboratories or kits are used, results can be used accurately to make vaccination decisions for some dogs and cats (Lappin et al., 2002). For example, previously vaccinated animals that were presumed to have had a vaccine reaction and are still at risk of exposure to infectious

agents could be assessed by serologic testing in lieu of arbitrary vaccination. In general, the positive predictive value of these tests is good (i.e., a positive test result usually predicts resistance on challenge).

#### **VACCINATION PROTOCOLS FOR CATS**

A physical examination, fecal parasite screen, and vaccine needs assessment should be performed at least yearly for all cats. The American Association of Feline Practitioners (AAFP) recently published the third version of the Feline Vaccine Advisory Panel Report (Richards et al., 2006; http://www.catvets.com). These guidelines are an excellent source of information for veterinarians to use when individualizing vaccination protocols. Vaccine antigens were divided into those that were considered core (FPV, FCV, FHV-1, and rabies), noncore (FeLV, FIV, Bordetella bronchiseptica, and Chlamydophila felis), and not generally recommended (Giardia and feline infectious peritonitis [FIP]). The following recommendations were adapted from the AAFP Panel Report.

#### **Core Vaccines**

Feline Panleukopenia Virus, Feline Calicivirus, Feline Immunodeficiency Virus-1. All healthy kittens and adult cats without a known vaccination history should be routinely vaccinated with an intranasal or parenteral vaccine that contains FPV, FCV, and FHV-1 (FVRCP). Multiple modified-live products and killed products are available, and the products available in the United States were recently reviewed (Richards et al., 2006). In general, modified-live FVRCP vaccines are recommended for kittens housed in environments at high risk for exposure to FPV. Modified-live FVRCP vaccines for intranasal administration can induce protection against FHV-1 as soon as 4 days after administration (Lappin and et al., 2006a), so this route of administration may be preferred for kittens housed in environments at high risk for exposure to FHV-1. Modified-live products should not be administered to clinically ill, debilitated, or pregnant animals. Owners should be informed that the administration of intranasal FVRCP vaccines can induce transient, mild sneezing or coughing.

For kittens believed to have no more than routine risk of exposure to FPV, FCV, or FHV-1, administration of FVRCP vaccines is recommended starting no sooner than 6 weeks of age, with boosters every 3 to 4 weeks until 16 weeks of age. Older kittens and adult cats with unknown vaccination history should receive two killed or two modified-live FVRCP doses 3 to 4 weeks apart.

For kittens believed to have high risk of exposure to FPV, such as those housed in animal shelters or pet stores, the AAFP panel currently recommends parenteral administration of modified-live FPV-containing vaccines as early as 4 weeks of age, particularly during an outbreak. However, intranasal administration of modified-live FVRCP vaccines instead of or in addition to parenteral administration of modified-live FVRCP vaccines may be superior for protection against FCV and FHV-1 in these environments.

The current AAFP Advisory Panel recommends a booster FVRCP vaccine 1 year later. However, a recent study showed that although no difference in FPV immunity occurred, the relative efficacy of FCV and FHV-1 vaccines were lower at 1 year after initial vaccination than at 4 weeks after initial vaccination (Poulet, 2007). The author concluded that the first FCV and FHV-1 booster vaccination after the completion of the initial series should be administered earlier than 1 year.

According to several challenge studies, administration of FVRCP vaccines does not appear to be needed more frequently than every third year after the 1-year booster vaccine; the duration of immunity may be much longer. As previously discussed, serologic test results for antibodies against FPV, FCV, and FHV-1 can be used to help determine vaccine needs (Lappin et al., 2002). (Validated serologic tests are available from New York State Veterinary Diagnostic Laboratory, Ithaca, and Heska Corporation, Loveland, Colo.)

Some variants of FCV induce systemic vasculitis in cats (virulent systemic calicivirus; VS-FCV), and clinical signs can be severe in some cats previously vaccinated with FVRCP vaccines (Hurley et al., 2004). A killed, VS-FCV-containing vaccine line is now available (Fort Dodge Animal Health, Overland Park, Kan.). Whether administration of this strain of FCV will be beneficial to cats is currently unknown. Factors to consider include the following. (1) The prevalence of VS-FCV infections is unknown and currently is believed to be rare. (2) The VS-FCV strains characterized to date have been genetically and antigenically distinct, so whether crossprotection among strains will occur is unknown. (3) The currently available vaccine line has only been shown to be effective against homologous challenge several weeks after completing the vaccine series, so the maximal duration of immunity is unknown. The AAFP recently published an informational brief on VJ-FCV (www.catvets.com). It is possible that use of two flu strains will help cross-protect against more flu strains than using one strain in vaccines.

Rabies. All cats should be vaccinated against rabies. Rabies vaccine should be administered subcutaneously in the distal right rear limb at the age recommended by the vaccine manufacturer (as early as 8 weeks depending on brand) in accordance with state and local statutes. Cats should be vaccinated 1 year later and then either annually or triennially according to state and local statutes and the vaccine product used. The currently available live virusvectored rabies vaccine (Merial, Duluth, Ga.) induces less inflammation than killed rabies vaccines, but whether this vaccine is less likely to be associated with soft tissue sarcomas is currently unknown.

## **Noncore Vaccines**

Bordetella bronchiseptica. The currently available Bordetella bronchiseptica vaccine for intranasal administration can be administered as early as 4 weeks of age, has an onset of immunity as early as 72 hours, and has a minimal duration of immunity of 1 year. Many cats have antibodies against B. bronchiseptica, the organism is commonly cultured from cats in crowded environments, and sporadic reports have been made of severe lower respiratory disease caused by bordetellosis in kittens and cats in crowded environments or other stressful situations. However, the significance of infection in otherwise healthy pet cats appears to be minimal. For example, in client-owned cats in northcentral Colorado, the organism was rarely cultured from cats with rhinitis or lower respiratory disease (approximately 3%). In addition, because the vaccine is administered by the intranasal route, mild sneezing and coughing can result. Bordetella vaccination should be considered primarily for use in cats at high risk for exposure and disease, such as those with a history of respiratory problems and living in shelters with culture-proven outbreaks. Because the disease is apparently not life threatening in adult cats, is uncommon in pet cats, and responds to a variety of antibiotics, routine use of this vaccine in client-owned cats seems unnecessary.

Chlamydophila felis. Killed and modified-live Chlamydophila felis-containing vaccines are available. Infection of cats by C. felis generally results in only mild conjunctivitis, is easily treated with antibiotics, has variable prevalence rates, and the organism is of minimal zoonotic risk to people. In addition, use of FVRCP vaccines that also contained C. felis was associated with more vaccine reactions in cats when compared with other products (Moore et al., 2007). Thus whether C. felis vaccination is ever necessary is controversial. The use of this vaccine should be reserved for cats with a high risk of exposure to other cats and in catteries with endemic disease. Duration of immunity for Chlamydophila vaccines may be short lived, so high-risk cats should be immunized before a potential exposure.

Feline Leukemia Virus. Several FeLV-containing vaccines are currently available. Some contain killed FeLV and an adjuvant, and others contain recombinant antigens of FeLV without adjuvant. In the United States the recombinant product is only available for delivery transdermally by a special device. Because of difficulties in assessing efficacy studies, which vaccine is optimal is unclear. The AAFP panel recommended vaccinating kittens for FeLV because they are more susceptible than adult cats, and their housing status may not have been determined at that time. Although administration of FeLV vaccines does not block proviral integration, FeLV-associated disease was lessened (Hofman-Lehmann et al., 2007). FeLV vaccines are most indicated in cats allowed to go outdoors or those who are exposed to cats of unknown FeLV status. Vaccinated cats should receive two vaccinations initially. Products with adjuvants should be administered subcutaneously in the distal left rear limb because of the risk for development of soft tissue sarcomas. Although the products without adjuvants are known to induce less inflammation, whether they are safer than the products containing adjuvants is currently unknown. Because little data are available concerning duration of immunity after 1 year, the AAFP Advisory Panel recommends annual boosters. The vaccine is not effective in persistently viremic cats and is therefore not indicated. However, administration of the vaccine to viremic or latently infected cats does not pose an increased risk of vaccine reaction. FeLV

testing should be performed before vaccination because the retrovirus serologic status of all cats should be known so appropriate husbandry can be maintained.

Feline Immunodeficiency Virus. A killed vaccine containing two FIV subtypes (clades A and D) is currently available for use in the United States (Fel-O-Vax FIV; Fort Dodge Animal Health). Administration of three doses, 3 to 4 weeks apart, starting no sooner than 8 weeks of age with annual boosters is currently recommended by the manufacturer. In prelicensing studies 689 cats received 2051 doses of vaccine, and adverse effects were detected in less than 1%. In a challenge study performed 375 days after inoculation with three doses (3 weeks apart), 84% of the vaccinated cats did not become infected with FIV, and 90% of the controls became infected, giving a preventable fraction of 82%. However, the efficacy and safety of the vaccine have not been assessed under field conditions in large numbers of cats exposed to multiple FIV subtypes (see Chapter 97). The primary problem with FIV vaccination at this time is that the vaccine induces antibodies detectable by the currently available antibody test. Thus after vaccination the practitioner will be unable to determine whether the cat is infected by FIV. Microchips are recommended so that owners of FIVvaccinated, seropositive cats can easily be found and euthanasia is not inadvertently performed because of the "FIV-positive status." Reverse-transcription polymerase chain reaction for detection of FIV provirus is available in some laboratories but, as discussed in Chapter 97, standardization and external quality control for laboratories providing this type of testing are not currently performed. The AAFP Advisory Panel recommends vaccinating only highrisk cats such as those that go outdoors and are known to fight and those housed with FIV-infected cats. Serologic testing should be performed before vaccination; the vaccine is not indicated in seropositive cats.

# **Vaccines not Generally Recommended**

Feline Infectious Peritonitis. A relatively safe coronavirus vaccine that may protect some cats from developing FIP is currently available for administration after 16 weeks of age. The vaccine may result in mild, transient sneezing because it is administered intranasally. Antibody-dependent enhancement of infectivity has not been detected in field studies. Results of the vaccine in field studies have been variable. If cats have previously been exposed to coronaviruses, the vaccine is unlikely to be effective (Fehr et al., 1997). Because the incidence of disease is low, cats are commonly exposed to coronaviruses before vaccination and the efficacy is questionable. The AAFP panel considered this vaccine as not generally recommended. The vaccine may be indicated for seronegative cats entering a known FIP-infected household or cattery.

**Giardia** spp. When administered twice, the currently available *Giardia* spp. vaccine lessened numbers of cysts shed and lessened clinical disease after challenge with one heterologous strain 1 year later. No published field studies currently prove the efficacy of the vaccine. In addition, multiple

Giardia spp. exist, including a feline-specific strain. Whether the vaccine is protective against strains other than the one used in challenge studies is unknown. In one study of experimentally infected cats, administration of three doses of the vaccine failed to change the course of cyst shedding with one strain of Giardia (Stein et al., 2003). Because giardiasis is usually not life threatening, typically responds to therapy, and vaccine efficacy has not been documented, the AAFP Advisory Panel considered this vaccine as not generally recommended.

#### **VACCINATION PROTOCOLS FOR DOGS**

A physical examination, fecal parasite screen, and vaccine needs assessment should be performed at least yearly for all dogs. The American Animal Hospital Association recently published the revised version of vaccination guidelines for dogs (Paul et al., 2006; http://www.aahanet.org/ PublicDocuments/VaccineGuidelines06Revised.pdf) that also included recommendations for use of canine vaccines in shelters. These guidelines are an excellent source of information for veterinarians to use when individualizing a vaccination protocol for dogs. Different forms of vaccine antigens were divided into those that were considered core, noncore, and not recommended. For two products (Crotalus atrox toxoid and Porphyromonas spp.), the Task Force chose to take no position because of a lack of experience and paucity of field validation of efficacy. The following discussion was adapted from those guidelines.

#### **Core Vaccines**

Canine Parvovirus, Canine Adenovirus, and Canine Distemper Virus. Because canine parvovirus (CPV-2), canine adenovirus 1 (CAV-1; infectious canine hepatitis), and canine distemper virus (CDV) can be lifethreatening diseases, all dogs should be vaccinated. For CPV-2, only modified-live products should be used because of increased risk of maternal antibody interference with killed products. Both modified-live CDV and recombinant CDV (rCDV)-containing vaccines are considered adequate by the AAHA Task Force. Because of adverse effects associated with CAV-1 vaccines and poor immune responses associated with killed CAV-2 or modified-live topical CAV-2 vaccines, only modified-live CAV-2 vaccines for parenteral administration should be used. These vaccines cross-protect against canine infectious hepatitis induced by CAV-1 and the kennel cough syndrome induced by CAV-2. All puppies should receive at least three CPV-2, CAV-2, and CDV-containing vaccines, every 3 to 4 weeks, between 6 and 16 weeks of age, with the last booster being administered at 14 to 16 weeks of age. Although one dose is likely protective, adult dogs with an unknown vaccination history can receive two doses 3 to 4 weeks apart. Puppies housed in shelters should be vaccinated on admission and then every 2 weeks while housed at the shelter or until 16 weeks of age. Vaccinated dogs should receive a booster vaccine 1 year later and then boosters at intervals of 3 years or longer. Several CDV-containing products, including the rCDV vaccine, were recently shown to

protect for at least 3 years (Abdelmagid et al., 2004; Larson et al., 2007).

Dogs should be evaluated at least yearly for risk of infection by CPV, CDV, and CAV during the physical examination and checked for enteric parasites. Positive serologic tests for CDV and CPV are predictive of resistance after challenge and can be used in lieu of arbitrary vaccine intervals if performed with validated assays. Dogs should complete the puppy series and be boosted at 1 year of age before using titers to help predict vaccine need. If the vaccination status of an adult dog is unknown, the dog should be vaccinated appropriately and then serologic assessment considered in subsequent years.

**Rabies.** All dogs should be vaccinated against rabies as early as 12 weeks of age. One-year and 3-year killed rabies products are available and should be administered according to the manufacturer's recommendations and state and local statutes. Both puppies and adult dogs with unknown vaccination history should be administered one dose and return for a booster vaccination 1 year later. Intervals and product after that booster should be based on state and local statutes.

#### **Noncore Vaccines**

**Bordetella bronchiseptica.** In general, *B. bronchiseptica* rarely causes life-threatening disease in otherwise healthy animals and is not the only cause of kennel cough syndrome. It is therefore considered a noncore vaccine. In addition, genetic information suggests that field strains of the bacterium vary considerably from vaccine strains, which may affect vaccine efficacy (Keil et al., 1999). Although parenteral products induce strong serum antibody responses, in one study intranasal administration was associated with superior protection on challenge (Davis et al., 2007). Booster vaccines should optimally be administered 7 days before potential exposure. No more than two boosters are needed per year.

Borrelia burgdorferi. The pros and cons of administering B. burgdorferi vaccines were discussed in depth in a recent American College of Veterinary Internal Medicine Consensus Statement (Littman et al., 2006; http://www. acvim.org). The AAHA Task Force suggested that B. burgdorferi vaccination only be considered in dogs with a known high risk of exposure (Paul et al., 2006). Depending on the product used, vaccination can start at 9 or 12 weeks of age and a second dose is recommended 2 to 4 weeks later, with annual boosters. Vaccination will not likely benefit a dog positive for antibody against the C6 peptide because most C6 antibody-positive dogs have already been infected. Whether vaccination protects against or is associated with Lyme nephropathy is unknown; the syndrome has been detected both in vaccinated and nonvaccinated dogs. Maintaining tick control is an important part of prevention of this disease.

**Distemper-Measles Virus.** This modified live product was used previously between 4 and 12 weeks of age to attempt to breakthrough maternal immunity to CDV. The need for this product is now in question because the rCDV vaccine immunizes puppies in the presence of maternal immunity.

Leptospira interrogans. Vaccines containing multiple Leptospira interrogans serovars (canicola, icterohaemorrhagiae, grippotyphosa, and pomona) are generally recommended for dogs with high risk in known endemic areas. However, some serovars in the environment are not in any vaccine, and minimal cross-protection exists between serovars. Thus clients should realize that even though their dog has been given a Leptospira vaccine, 100% protection cannot be guaranteed. Newer generation vaccines have fewer adverse effects than previous vaccines. If the vaccines are to be used, puppies should receive the first dose at 12 weeks of age with a booster 2 to 4 weeks later. Adults should receive two doses 2 to 4 weeks apart. Annual revaccination is recommended for vaccines containing the four serovars.

**Parainfluenza Virus.** Multiple products that contain CPV-2, CDV, and CAV-2 also contain modified-live parainfluenza, so they are commonly administered at the same schedule of those core vaccine antigens. Considered alone, parainfluenza is noncore because it is not life threatening, is not zoonotic, and is a self-limited cause of kennel cough syndrome. A modified-live strain for intranasal administration combined with a live avirulent strain of *B. bronchiseptica* is also available. If used, the intranasal vaccine can be administered as early as 3 weeks of age; transient sneezing and coughing can occur. Booster vaccines are administered following the same schedule as the antigens in which parainfluenza is combined.

#### Not Recommended

As previously discussed, killed CPV-2 vaccines, MLV or killed CAV-1 vaccines, killed CAV-2 vaccines, and modified-live CAV-2 vaccines for topical administration are considered not recommended by the AAHA Task Force. The following vaccines are also considered not recommended.

**Coronavirus.** Coronavirus infection in dogs results in mild gastrointestinal disease unless concurrent infection with parvovirus occurs. The virus rarely causes disease in dogs after 6 weeks of age. In one study of healthy dogs and dogs with diarrhea, coronavirus was only detected in one healthy dog. Based on these findings, vaccination against coronavirus is not indicated in dogs.

Giardia spp. When administered twice, the currently available Giardia spp. vaccine lessened numbers of cysts shed and lessened clinical disease after challenge with one heterologous strain 1 year later. Several field studies of the vaccine have been carried out in dogs; none has documented lessening of giardiasis in asymptomatic dogs (Anderson et al., 2004). Dog-specific Giardia strains have become apparent; vaccine efficacy against these strains is unknown. Because giardiasis is usually not life threatening, typically responds to therapy, and vaccine efficacy has not been documented, the AAHA Task Force considers this vaccine to not be generally recommended. In one study of 17 dogs with resistant giardiasis, cyst shedding and diarrhea resolved in all dogs after administration of two doses of Giardia vaccine, so it may be effective as an immunotherapy in some dogs (Olson et al., 2001).

#### Insufficient Information

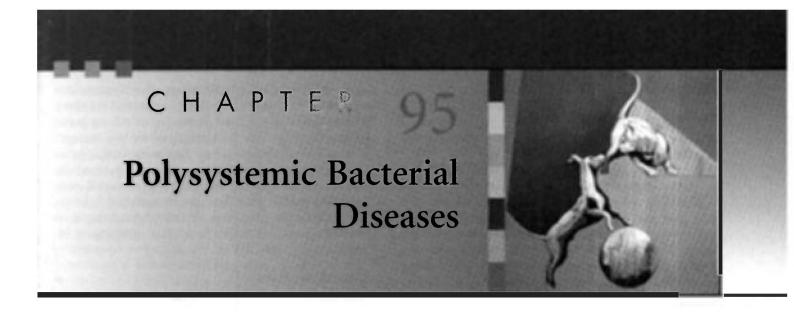
**Periodontal Disease Vaccine.** The *Porphyromonas* spp. vaccine is designed to aid in the prevention and control of periodontal disease in dogs. Because efficacy has not been determined, the AAHA Task Force declined to take a position on this vaccine (Paul et al., 2006).

**Rattlesnake Vaccine.** The *Crotalus atrox* toxoid vaccine was designed to protect dogs against the venom of the Western Diamondback Rattlesnake. Some cross-protection may exist against the Eastern Diamondback Rattlesnake but not the Mojave Rattlesnake. Local reactions to this toxoid are common. Because efficacy has not been determined, the AAHA Task Force declined to take a position on this vaccine (Paul et al., 2006).

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# CHAPTER OUTLINE

CANINE BARTONELLOSIS
FELINE BARTONELLOSIS
FELINE PLAGUE
LEPTOSPIROSIS
MYCOPLASMA AND UREAPLASMA

# CANINE BARTONELLOSIS

# **Etiology and Epidemiology**

Bartonella vinsonii subspecies berkhoffii was initially isolated from a dog with endocarditis in North Carolina (Breitschwerdt et al., 1995). Since that time, dogs in multiple areas of the world have been shown to seroreact with B. vinsonii (berkhoffii) antigens. B. vinsonii (berkhoffii) is thought to be tickborne. Serum of some infected dogs also seroreacts with B. henselae and B. clarridgeiae antigens; these Bartonella species are transmitted by fleas. Bartonella species that have been isolated from dogs or from which DNA has been amplified from blood or tissues include B. vinsonii (berkhoffii), B. henselae, B. clarridgeiae, B. washoensis, B. quintana, and B. elizabethae. Each of these organisms potentially can induce illness in dogs. Dogs infected with a Bartonella species are commonly coinfected with other agents, such as Anaplasma spp. or Ehrlichia spp., which may play a role in the pathogenesis of disease.

# **Clinical Features**

Clinical findings or syndromes most frequently attributed to *Bartonella* spp. infections of dogs include endocarditis, fever, arrhythmias, hepatitis, granulomatous lymphadenitis, cutaneous vasculitis, rhinitis, polyarthritis, meningoencephalitis, thrombocytopenia, eosinophilia, monocytosis, immunemediated hemolytic anemia, epistaxis, and uveitis. *B. vinsonii* (berkhoffii) and *B. henselae* seem to be the most likely species

to be associated with clinical disease (Breitschwerdt et al., 2004; Goodman and Breitschwerdt, 2005; Henn et al., 2005). In one study of valvular endocarditis, all dogs with *Bartonella* spp.—associated disease were also seropositive for *Anaplasma phagocytophilum* (MacDonald et al., 2004). Whether the coinfection potentiated the *Bartonella*-associated disease is unknown.

# Diagnosis

Serum antibodies can be detected in both healthy and clinically ill dogs, so the presence of antibodies does not always correlate to illness. Some *Bartonella* species, in particular *B. vinsonii (berkhoffii)*, can be difficult to culture; amplification of DNA by polymerase chain reaction (PCR) assay with or without culture is often needed to confirm infection (Duncan et al., 2007). If positive test results are detected in a clinically ill dog and no other explanation for the illness is obvious, treatment is indicated.

#### **Treatment**

Because many cases of bartonellosis in dogs have been apparently resistant to administration of doxycycline, some clinicians believe that azithromycin is the treatment of choice. Fluoroquinolones, alone or in combination with azithromycin, were apparently effective for the treatment of some dogs with suspected clinical bartonellosis. Rifampin may be required for resistant cases. No matter which drug is used, a minimum of 4 to 6 weeks of treatment is usually needed. In one study successfully treated dogs became seronegative (Breitschwerdt et al., 2004).

# **Zoonotic Aspects and Prevention**

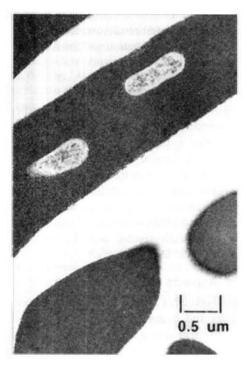
B. vinsonii (berkhoffii) and B. henselae have been detected in both dogs and human beings, and cat scratch disease has been documented in a human being after exposure to a dog (Chen et al., 2007). Care should be taken to avoid bites or scratches while handling or treating infected dogs. Flea and tick control is likely to lessen transmission of Bartonella species between dogs and perhaps from dogs to people.

# **FELINE BARTONELLOSIS**

# **Etiology and Epidemiology**

Cats have been proven to be infected by B. henselae, B. clarridgeiae, B. koehlerae, B. quintana, and B. bovis by culture or DNA amplification (Brunt et al., 2006). Antibodies against B. elizabethae have been detected in some cats, but these results should be interpreted cautiously because of the serologic cross-reactivity among Bartonella spp. Cats are the main reservoir hosts for B. henselae and B. clarridgeiae and are likely the reservoir for B. koehlerae. B. henselae is the most common cause of cat scratch disease as well as bacillary angiomatosis and peliosis hepatis, common disorders in human beings with acquired immunodeficiency syndrome. Bartonella species have both intraendothelial and intraerythrocytic phases of infection (Fig. 95-1). The intracellular location may relate to the difficulties in permanently eliminating bacteremia (Kordick and Breitschwerdt, 1995; Seubert et al., 2002).

On the basis of results of seroprevalence studies, culture, or PCR assay, cats are commonly exposed to or infected by *Bartonella* species. The organism is transmitted between cats by *Ctenocephalides felis*, so prevalence is greatest in cats from regions where fleas are common. A recent study in the United States collected fleas from cats and attempted to amplify *Bartonella* species DNA from flea digests as well as the blood of the cat (Lappin et al., 2006). The prevalence rates for *B. henselae* in cats and their fleas were 34.8% and 22.8%, respectively. The prevalence rates for *B. clarridgeiae* in cats and



**FIG 95-1** Electron micrograph of a feline erythrocyte showing intracellular *Bartonella henselae*. (Courtesy Dr. Dorsey Kordick.)

their fleas were 20.7% and 19.6%, respectively. Results have been similar in other studies performed around the world. *B. henselae* survives in flea feces for days after being passed by infected *C. felis*. Infected flea feces are likely to contaminate cat claws during grooming, then *Bartonella* species are inoculated into the person when scratched. Open wounds also may be contaminated with infected flea feces. However, *Bartonella* species DNA can also be amplified from the mouths of healthy cats and those with gingivostomatitis, so bites and scratches should be avoided (Quimby et al., 2007).

#### **Clinical Features**

Most cats with serologic evidence of exposure to Bartonella spp., Bartonella spp. cultured from blood, or microbial DNA amplified from blood by PCR assay are clinically normal. However, Bartonella spp. infection of cats has also been associated directly or indirectly with a variety of clinical manifestations such as fever, lethargy, lymphadenopathy, uveitis, gingivitis, and neurologic diseases. How often cats become ill from Bartonella spp. infections is unknown, and more information is needed. For example, the association of B. henselae infection to uveitis in a cat was first made in an individual case with uveitis that ultimately responded to doxycycline therapy (Lappin and Black, 1999; Lappin et al. 2000) subsequently found Bartonella antibody production and DNA in the aqueous humor of cats previously presumed to have idiopathic uveitis. A series of clinical cases of feline ocular disease that were responsive to antibiotic therapy was recently reported (Ketring et al., 2004). Thus Bartonella species appears to cause ocular disease in some cats. However, which cats have been exposed and which cats are diseased can be difficult to determine. In one study of feral cats in North Carolina the seroprevalence rate was 93% (Nutter et al., 2005). In another study the presence of Bartonella species antibodies failed to correlate to the presence of most clinical syndromes in ill cats (Breitschwerdt et al., 2005b). In recent studies in the author's laboratory, the prevalence rates for Bartonella species antibodies in feline sera were not significantly different for cats with or without seizures (Pearce et al., 2006) or cats with or without stomatitis (Dowers et al., 2005). Why some cats develop Bartonella-associated illness and others do not is still not clear. For example, Powell et al. (2002) failed to induce Toxoplasma gondii or Bartonella species uveitis when Bartonella was intravenously inoculated into cats with chronic toxoplasmosis.

#### Diagnosis

Blood culture, PCR assay on blood, and serologic testing can be used to assess individual cats for *Bartonella* spp. infection. Cats that are culture negative or PCR negative and antibody negative and cats that are culture negative or PCR negative and antibody positive are probably not a source of flea, cat, or human infection. However, bacteremia can be intermittent and false-negative culture or PCR results can occur, limiting the predictive value of a single battery of tests. False-positive results can occur with PCR, and positive results do

not necessarily indicate that the organism is alive. Although serologic testing can be used to determine whether an individual cat has been exposed, both seropositive and seronegative cats can be bacteremic, limiting the diagnostic utility of serologic testing. Thus testing healthy cats for Bartonella spp. infection is not currently recommended (Brunt et al., 2006). Testing should be reserved for cats with suspected clinical bartonellosis. If the results of Bartonella tests are negative in a clinically ill cat, the organism is not likely the cause of the clinical syndrome unless the infection was peracute and serologic testing was used as the diagnostic test. If the results of Bartonella tests are positive, the agent remains on the list of differential diagnoses, but other causes of the clinical syndrome must also be excluded. The American Association of Feline Practitioners (AAFP) Bartonella Panel Report suggests that the diagnosis of clinical bartonellosis include the following combination of findings (Brunt et al., 2006):

- · Presence of a syndrome reported to be associated with Bartonella spp. infection
- · Exclusion of other causes of the clinical syndrome
- Detection of a positive Bartonella spp. test (culture, PCR assay, or serology)
- Response to administration of a drug with presumed anti-Bartonella activity

However, fulfillment of these criteria does not always prove a definitive diagnosis. The antibiotics used for the treatment of bartonellosis in cats generally have a broad spectrum, are effective for other infecting organisms that can cause syndromes resembling bartonellosis, and can also have antiinflammatory properties.

#### **Treatment**

In experimental studies administration of doxycycline, tetracycline, erythromycin, amoxicillin-clavulanate, and enrofloxacin can limit bacteremia but does not cure infection in all cats. To date, use of antibiotics in healthy cats has not been shown to lessen the risk of cat scratch disease (Brunt et al., 2006). In addition, treating healthy cats with antibiotics that do not eliminate infection may predispose to resistant stains of the organism. Thus in the United States treatment is generally recommended for clinically ill cats. If clinical bartonellosis is suspected, the AAFP Panel Report recommends doxycycline at 10 mg/kg PO daily for 7 days as the initial therapeutic trial (Brunt et al., 2006). Doxycycline should be formulated into a flavored suspension or water should be administered after pilling to avoid esophageal strictures. If a beneficial response is achieved, continue treatment for 2 weeks past clinical resolution of the disease or for a minimum of 28 days. If a poor response is achieved by day 7 or doxycycline is not tolerated and bartonellosis is still a valid differential diagnosis, azithromycin or a fluoroquinolone is a good second choice. Other differential diagnoses should be considered for Bartonella spp.-positive cats that have not responded after administration of two different drugs with presumed anti-Bartonella activity. Because cats can be reinfected with Bartonella spp., clinical value to following results of Bartonella spp. tests seems to be minimal if the cat is clinically normal.

# **Zoonotic Aspects and Prevention**

Bartonella spp. infections are an occupational risk for veterinary health care providers (Breitschwerdt et al., 2007). To lessen the likelihood of acquiring a Bartonella species infection from a cat, the following adaptations of recommendations to HIV-infected people and other cat owners by the Centers for Disease Control and Prevention and the American Association of Feline Practitioners have been developed:

- · Flea control should be initiated and maintained year round
- If a family member is immunocompromised and a new cat is to be acquired, adopt a healthy cat older than 1 year and free of fleas.
- · Immunocompromised individuals should avoid contact with cats of unknown health status.
- · Declawing of cats is generally not required, but claws should be trimmed regularly.
- Bites and scratches should be avoided (including rough play with cats).
- Cat-associated wounds should be washed promptly and thoroughly with soap and water and medical advice
- · Although Bartonella species have not been shown to be transmitted by saliva, cats should not be allowed to lick open wounds.
- · Keep cats indoors to minimize hunting and exposure to fleas and other possible vectors.

The Centers for Disease Control and Prevention do not recommend testing or treating healthy cats for Bartonella spp. infections.

# **FELINE PLAGUE**

# **Etiology and Epidemiology**

Yersinia pestis is the facultatively anaerobic gram-negative coccobacillus that causes plague. The organism is maintained in a sylvan life cycle between rodent fleas and infected rodents, including rock squirrels, ground squirrels, and prairie dogs. Cats are susceptible to infection and can die after natural or experimental infection; dogs are highly resistant to infection. Antibodies against Y. pestis are also detected in serum of nondomestic felids (Biek et al., 2006). Clinical disease is recognized most frequently from spring through early fall, when rodents and rodent fleas are most active. Most of the cases in human beings and cats have been documented in Colorado, New Mexico, Arizona, California, and Texas (Undisclosed authors, 2006). Of the cases of human plague diagnosed from 1977 to 1998, 23 (7.7%) resulted from contact with infected cats (Gage et al., 2000).



BOX 95-1

Clinical Findings in Cats with Yersinia pestis Infection (Plague)

#### **Signalment**

All ages, breeds, and gender

#### **History and Physical Examination**

Outdoor cats

Male cats

Hunting of rodents or exposure to rodent fleas

Depression

Cervical swellings, draining tracts, lymphadenopathy Dyspnea or cough

#### Clinicopathologic and Radiographic Evaluation

Neutrophilia with or without a left shift Lymphopenia

Neutrophilic lymphadenitis or pneumonitis

Homogenous population of bipolar rods cytologically (lymph node aspirate or airway washings)

Serum antibody titers, either negative (peracute) or positive

Interstitial and alveolar lung disease

#### Diagnosis

Culture of blood, exudates, tonsillar region, respiratory secretions

Fluorescent antibody identification of organism in exudates

Fourfold increase in antibody titer and appropriate clinical signs

Cats are infected after being bitten by infected rodent fleas, after ingestion of bacteremic rodents, or after inhalation of the organism. After ingestion, the organism replicates in the tonsils and pharyngeal lymph nodes, disseminates in the blood, and results in a neutrophilic inflammatory response and abscess formation in infected tissues. The incubation period is 2 to 6 days after a flea bite and 1 to 3 days after ingestion or inhalation of the organism. Outcomes in experimentally infected cats include death (six of 16 cats; 38%), transient febrile illness with lymphadenopathy (seven of 16 cats; 44%), or inapparent infection (three of 16 cats; 18%) (Gasper et al., 1993).

#### **Clinical Features**

Bubonic, septicemic, and pneumonic plague develop in infected human beings and cats (Box 95-1); clinical disease is extremely rare in dogs (Orloski et al., 1995). Bubonic plague is the most common form of the disease in cats, but individual cats can show clinical signs of all three syndromes. Most infected cats are housed outdoors and have a history of hunting. Anorexia, depression, cervical swelling, dyspnea, and cough are common presenting complaints; fever is detected in most infected cats. Unilateral or bilateral enlarged tonsils, mandibular lymph nodes, and anterior cervical

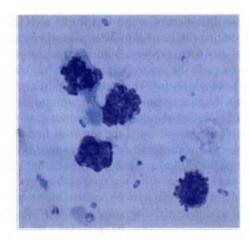


FIG 95-2 Lymph node aspirate from a cat with bubonic plague stained with Wright's stain. Bipolar rods are scattered throughout the field.

lymph nodes are detected in approximately 50% of infected cats. Cats with pneumonic plague commonly have respiratory signs and may cough.

# **Diagnosis**

Hematologic and serum biochemical abnormalities reflect bacteremia and are not specific for *Y. pestis* infection. Neutrophilic leukocytosis, left shift and lymphopenia, hypoalbuminemia, hyperglobulinemia, hyperglycemia, azotemia, hypokalemia, hypochloremia, hyperbilirubinemia, and increased activities of alkaline phosphatase and alanine transaminase are common. Pneumonic plague causes increased alveolar and diffuse interstitial densities on thoracic radiographs. Cytologic examination of lymph node aspirates reveals lymphoid hyperplasia, neutrophilic infiltrates, and bipolar rods (Fig. 95-2).

Cytologic demonstration of bipolar rods on examination of lymph node aspirates, exudates from draining abscesses, or airway washings combined with a history of potential exposure, the presence of rodent fleas, and appropriate clinical signs lead to a presumptive diagnosis of feline plague. Because some cats survive infection and antibodies can be detected in serum for at least 300 days, detection of antibodies alone may indicate only exposure, not clinical infection. However, demonstration of a fourfold increase in antibody titer is consistent with recent infection. A definitive diagnosis is made by culture or fluorescent antibody demonstration of *Y. pestis* in smears of the tonsillar region, lymph node aspirates, exudates from draining abscesses, airway washings, or blood.

#### **Treatment**

Supportive care should be administered as indicated for any bacteremic animal (see Chapter 93). Cervical lymph node abscesses should be drained and flushed with the clinician wearing gloves, a mask, and a gown. Parenteral antibiotics should be administered until anorexia and fever resolve.

Optimal antibiotics for treatment of plague in infected cats in the United States are unknown. Streptomycin administered intramuscularly at 5 mg/kg q12h was used historically but is not widely available. Cats treated with gentamicin intramuscularly or intravenously at 2 to 4 mg/kg q12-24h, or enrofloxacin intramuscularly or intravenously at 5.0 mg/ kg q24h, has resolved clinical signs. Chloramphenicol administered orally or intravenously at 15 mg/kg q12h can be used in cats with central nervous system signs. Antibiotics should be administered orally for 21 days after the cat has survived the bacteremic phase; doxycycline at 5 mg/kg q12-24h or tetracycline at 20 mg/kg q8h is an appropriate choice. Care should be taken to avoid tetracycline-associated esophageal strictures by giving water after drug administration or liquefying the product. In one study 90.9% of cats treated with antibiotics survived, whereas only 23.8% of untreated cats survived (Eidson et al., 1991). The prognosis is poor for cats with pneumonic or septicemic plague.

# **Zoonotic Aspects and Prevention**

Cats should be housed indoors and not allowed to hunt. Flea control should be used and the rodent population should be controlled if possible. Tetracycline or doxycycline at the doses listed for therapy should be administered for 7 days to animals with potential exposure. Human infection occurs after contact with infected fleas; contact with the tissues or exudates from infected animals, including cats; and from bites and scratches from infected cats. Even though fomite transmission is unlikely, because the organism is sensitive to drying it can survive for weeks to months in infected carcasses and for up to 1 year in infected fleas. Cats from endemic areas with clinical signs of bacteremia, respiratory tract disease, or cervical draining areas or masses in the spring, summer, and early fall months should immediately be treated for fleas and handled with the clinician wearing gloves, a mask, and a gown until the diagnosis is made or discarded. While hospitalized, infected cats should be handled by as few personnel as possible while in isolation. Exposed people should see their physicians to discuss prophylactic antibiotic therapy; antimicrobial-resistant strains of Y. pestis are uncommon (Welch et al., 2007). Cats are not infectious to human beings after 3 days of antibiotic therapy. Areas where infected cats are handled should be thoroughly cleaned with routine disinfectants (see Chapter 94).

#### LEPTOSPIROSIS

# **Etiology and Epidemiology**

Leptospires are 0.1 to 0.2 μm wide by 6 to 12 μm long, motile, filamentous spirochetes that infect animals and human beings. Leptospirosis can be caused by many different serovars of Leptospira interrogans and L. kirschneri (Table 95-1). Seropositive dogs have been detected in many countries, and the most prevalent serovars vary by country and regions within countries. In the United States antibodies against L. autumnalis, L. bratislava, L. canicola, L. grippoty-



TABLE 95-1

Reservoirs for Leptospira Serovars Known to Infect Dogs

SEROVAR	PRIMARY RESERVOIR
L. bataviae L. bratislava L. canicola L. grippotyphosa L. harjo L. icterohaemorrhagiae L. pomona L. tarassovi	Dog, rat, mouse Pig, horse, dog Dog Vole, raccoon, skunk, opossum Cow Rat Pig, skunk, opossum Cow, pig

phosa, L. hardjo, L. icterohaemorrhagiae, and L. pomona have been detected most commonly. Cats are infected by L. bratislava, L. canicola, L. grippotyphosa, and L. pomona but appear to be resistant to clinical disease.

Prevalence and risk factors for cases of canine leptospirosis have been evaluated in several studies in the last few years (Ward et al., 2002; Boutilier et al., 2003; Ward et al., 2004ab; Goldstein et al., 2006; Ghneim et al., 2007; Stokes et al., 2007). In the United States the number of seropositive dogs increased between 2002 and 2004 (Moore et al., 2006). Infection by leptospires occurs in both rural and suburban environments in semitropical areas of the world with alkaline soil conditions. Exposure to water outdoors, wetlands, and public open spaces were identified as risk factors in one case-control study (Ghneim et al., 2006). Clinical cases are most commonly diagnosed in the summer and early fall, and numbers of cases often increase in years with heavy rainfall. Infection by host-adapted species results in subclinical infection; the host acts as a reservoir, shedding the organism intermittently. Infection by non-host-adapted species results in clinical illness. Leptospires are passed in urine and enter the body through abraded skin or intact mucous membranes. Transmission also occurs through bite wounds; by venereal contact; transplacentally; and by ingestion of contaminated tissues, soil, water, bedding, food, and other fomites. In a recent experimental study L. pomona but not L. bratislava was successfully transmitted by conjunctival inoculation and resulted in fever and lethargy starting within 7 days (Greenlee et al., 2005). Hosts with preexisting antibody titers usually eliminate the organism quickly and remain subclinically infected. Leptospires replicate in multiple tissues of nonimmune hosts or hosts infected by a non-host-adapted species; in the dog the liver and kidneys develop the highest levels of infection. Inflammation induced by organism replication and production of toxins leads to renal, hepatic, or pulmonary disease. Dogs that are treated or develop appropriate immune responses usually survive. Some animals clear the infection 2 to 3 weeks after exposure without treatment but develop chronic active hepatitis or chronic renal disease. Cats are generally subclinically affected but may shed the organism into the environment for variable periods after exposure.

# **Clinical Findings**

Dogs of any age or breed or either gender can develop leptospirosis if not previously immune. Male, middle-aged, herding dogs; hounds; working dogs; and mixed breeds are at greater risk than companion dogs younger than 1 year (Ward et al., 2002). Most dogs have subclinical infection. Dogs with peracute clinical disease are usually presented for evaluation of anorexia, depression, generalized muscle hyperesthesia, tachypnea, and vomiting (Box 95-2). Fever,



BOX 95-2

Clinical Findings in Dogs with Leptospirosis

#### Signalment

All ages, breeds, and gender Greatest risk in young adult, male, working dogs

#### History

Exposure to appropriate reservoir host or contaminated environment

Anorexia, depression, lethargy

#### **Physical Examination**

Fever

Anterior uveitis

Hemorrhagic tendencies, including melena, epistaxis, petechiae, and ecchymoses

Vomiting, diarrhea

Muscle or meningeal pain

Renomegaly with or without renal pain

Hepatomegaly

Polyuria/polydipsia

lcterus

Coughing or respiratory distress

#### Clinicopathologic and Radiographic Evaluation

Thrombocytopenia

Leukopenia (acute)

Leukocytosis (subacute)

Azotemia

Suboptimal urine concentrating ability

Pyuria and hematuria without obvious bacteriuria

Hyperbilirubinemia and bilirubinuria

Increased activities of alanine transaminase, aspartate transaminase, alkaline phosphatase, and creatine kinase

Interstitial to alveolar lung disease

Hepatomegaly or renomegaly

#### Diagnosis

Culture of urine, blood, or tissues

Demonstration of the organism in urine by darkfield or phase-contrast microscopy

Demonstration of organismal DNA in urine, blood, or tissues by PCR

Combination of increasing antibody titer with clinical signs and response to therapy

pale mucous membranes, and tachycardia are usually present. Petechiae, ecchymoses, melena, and epistaxis occur frequently from thrombocytopenia and disseminated intravascular coagulation. Peracute infections may rapidly progress to death before marked renal or hepatic disease is recognized.

Fever, depression, and clinical signs or physical examination findings consistent with hemorrhagic syndromes, hepatic disease, renal disease, or a combination of hepatic and renal disease are common in subacutely infected dogs. Conjunctivitis, panuveitis, rhinitis, tonsillitis, cough, and dyspnea occur occasionally. Oliguric or anuric renal failure can develop during the subacute phase. Clinical findings can vary based on the infecting serovar (Goldstein et al., 2006).

Some dogs that survive peracute or subacute infection develop chronic interstitial nephritis or chronic active hepatitis. Polyuria, polydipsia, weight loss, ascites, and signs of hepatic encephalopathy secondary to hepatic insufficiency are the most common manifestations of chronic leptospirosis.

# **Diagnosis**

Multiple nonspecific clinicopathologic and radiographic abnormalities occur in dogs with leptospirosis and vary depending on the host, the serovar, and whether the disease was peracute, subacute, or chronic. Leukopenia (peracute leptospiremic phase), leukocytosis with or without a left shift, thrombocytopenia, regenerative anemia (from blood loss), or nonregenerative anemia (from chronic renal or hepatic disease) are common hematologic abnormalities. Hyponatremia; hypokalemia; hyperphosphatemia; hypoalbuminemia; hypocalcemia; azotemia; hyperbilirubinemia; decreased total carbon dioxide concentrations; and increased activities of alanine transaminase, alkaline phosphatase, and aspartate transaminase are common serum biochemical abnormalities that develop from renal disease, hepatic disease, gastrointestinal losses, or acidosis. Hyperglobulinemia is detected in some dogs with chronic leptospirosis. Dogs with myositis may have increased creatine kinase activity. Urinalysis abnormalities include bilirubinuria, suboptimal urine specific gravity in the face of azotemia, granular casts, and increased numbers of granulocytes and erythrocytes. The organism is not seen in the urine sediment by light microscopy. Renomegaly, hepatomegaly, and interstitial or alveolar pulmonary infiltrates are common radiographic abnormalities. Mineralization of the renal pelves and cortices can occur with chronic leptospirosis.

Detection of anti-Leptospira antibodies is commonly performed by a microscopic agglutination test. Because of the wide range of leptospires infecting dogs, as many serovars as possible should be used for screening. L. bratislava, L. canicola, L. grippotyphosa, L. hardjo, L. icterohaemorrhagiae, and L. pomona are commonly used. Positive titers can result from active infection, previous infection, or vaccination. Antibody titers can be negative in animals with peracute disease; seronegative dogs with classic clinical disease should be retested in 2 to 4 weeks. The serovar with the highest titer is usually considered the infecting serovar, but this should be

interpreted cautiously. When the same sera were sent to different laboratories, the results were not always in agreement for the serovar giving the highest titer (Miller et al., 2007).

Documentation of seroconversion (negative result becoming positive over time), a single microscopic agglutination test titer greater than 1:3200, or a fourfold increase in antibody titers combined with appropriate clinicopathologic abnormalities and clinical findings, are suggestive of clinical leptospirosis. A definitive diagnosis is made by demonstrating the organism in urine, blood, or tissues. The organism can be seen in urine using darkfield or phasecontrast microscopy, but because of intermittent shedding of small numbers of organisms these procedures can be falsely negative. The organism can be cultured from urine collected by cystocentesis, blood, or renal or hepatic tissue. Materials for culture should be collected before administration of antibiotics, placed in transport media immediately after collection, and transported to the laboratory as quickly as possible. Leptospiremia can be of short duration, and urine shedding of the organism can be intermittent, giving false-negative results. PCR can be used to demonstrate the organism in urine, blood, or tissues (Harkin et al., 2003a, 2003b). In one study of 500 dogs, 41 (8.2%) were PCR positive for a Leptospira spp. in urine, and some of these dogs were clinically normal (Harkin et al., 2003a). None of the PCR-positive dogs was culture positive, and titers were not always elevated.

#### Treatment

Fluid therapy is required for most dogs; intense diuresis for renal involvement may be required (see Chapter 44). Hemodialysis may increase the probability of survival in dogs with oliguric or anuric renal failure. Dogs should be treated during the initial treatment period with ampicillin administered intravenously at 22 mg/kg q8h or penicillin G administered intramuscularly or intravenously at 25,000 to 40,000 U/kg q12h. Some quinolones have an effect against leptospires and can be used in combination with penicillins during the acute phase of infection. Ampicillin and enrofloxacin were used concurrently in one study; 83% of infected dogs survived (Adin et al., 2000). Penicillins such as amoxicillin or amoxicillin clavulanate should be administered for 2 weeks. Doxycycline administered orally at 2.5 to 5.0 mg/kg q12h for 2 weeks after penicillin therapy should be used to eliminate the renal carrier phase.

# **Zoonotic Aspects and Prevention**

All mammalian serovars should be considered potentially zoonotic to human beings. Some human beings have antibodies against canine serovars, suggesting the dog can be a reservoir for human infection (Brod et al., 2005). Infected urine, contaminated water, and reservoir hosts should be avoided. Infected dogs should be handled with the clinician wearing gloves. Contaminated surfaces should be cleaned with detergents and disinfected (see Chapter 94).

To lessen risk of exposure, owners should attempt to restrict dogs from drinking potentially contaminated water.

Vaccines available for some serovars reduce the severity of disease. Vaccination against serovars *L. canicola* and *L. ictero-haemorrhagiae* can induce serologic cross-reactivity against serovars not contained in the vaccine, but cross-protection against other serovars is not always induced (Barr et al., 2005). Products containing serovars *L. canicola*, *L. ictero-haemorrhagiae*, *L. grippotyphosa*, and *L. pomona* are now available and provide the greatest spectrum of protection (see Chapter 94). Vaccination can lessen shedding of leptospires in the urine; not all vaccines perform the same (Andre-Fontaine et al., 2003; Schreiber et al., 2005). Dogs in endemic areas should receive three vaccinations 2 to 3 weeks apart. The duration of immunity is longer than 1 year in dogs receiving three vaccinations.

# MYCOPLASMA AND UREAPLASMA

# **Etiology and Epidemiology**

Mycoplasma spp. and Ureaplasma spp. are small, free-living microorganisms that lack a rigid, protective cell wall and depend on the environment for nourishment. Some Mycoplasma spp. and Ureaplasma spp. are considered normal flora of mucous membranes. For example, Mycoplasma spp. have been isolated from the vagina of 75% of healthy dogs (Doig et al., 1981), the pharynx of 100% of healthy dogs, and the pharynx of 35% of healthy cats (Randolph et al., 1993). Haemobartonella felis and H. canis were recently shown to be Mycoplasmas. Cats are infected by three species, M. haemofelis, "Candidatus M. haemominutum," and "Candidatus M. turicensis." Dogs are infected by two species, M. haemocanis and Candidatus M. haematoparvum. These organisms are associated with red blood cells and may result in the development of anemia. These organisms are discussed in Chapter 85.

M. felis conjunctivitis in cats, M. felis upper respiratory tract infection in cats, M. gateae polyarthritis in cats, and M. cynos pneumonia in dogs have been induced experimentally. The pathogenic potential for most Mycoplasma spp. or Ureaplasma spp. is difficult to determine because the organisms can be cultured or amplified from both healthy and sick animals. In many cases Mycoplasma spp. or Ureaplasma spp. may be colonizing diseased tissues as opportunists as a result of inflammation induced by other causes. Other bacteria are usually isolated concurrently with Mycoplasma spp. or Ureaplasma spp., making it difficult to determine which agent is inducing disease. Ureaplasma spp. have been cultured from the vagina (40%) and prepuce (10%) of healthy dogs (Doig et al., 1981).

Mycoplasma spp. were isolated in pure culture from 20 of 2900 dogs with clinical signs of urinary tract inflammation (Jang et al., 1984), M. canis was isolated from four of 100 dogs (three in pure culture) with clinical signs of lower urinary tract disease (Ulgen et al., 2006), and M. canis was isolated from nine dogs with clinical signs of urogenital disease (L'Abee-Lund et al., 2003). Some M. canis—infected dogs were azotemic, suggesting pyelonephritis (Ulgen et al.,

2006), and some have been resistant to therapy (L'Abeelund et al., 2003). Multiple studies suggest that some *Mycoplasma* spp. can be primary pathogens of the respiratory tract of dogs. *Mycoplasma* spp. were the only organism cultured from seven of 93 dogs (Jameson et al., 1995), five of 38 dogs (Randolph et al., 1993), and 14 dogs (Chandler et al., 2002) with lower respiratory tract disease. In one study that compared *Mycoplasma* isolates from dogs with and without respiratory disease, *M. cynos* in the lower respiratory tract was statistically associated with respiratory disease (Chalker et al., 2004b). In another study, 80% of dogs that developed antibodies to *M. cynos* had respiratory signs of disease (Rycroft et al., 2007).

In a recent study of cats with and without conjunctivitis, the presence of *Mycoplasma* spp. DNA was associated with the presence of conjunctivitis (Low et al., 2007). Both *M. felis* and *M. gateae* have been associated with feline ulcerative keratitis (Gray et al., 2005). *M. gateae* and *M. felis* have been detected in cats with polyarthritis. *Mycoplasma* spp. have also been associated with the presence of rhinosinusitis (Johnson et al., 2005; Bannasch et al., 2005), lower respiratory disease (Randolph et al., 1993; Chandler et al., 2002; Foster et al., 2004a, 2004b), and pyothorax (Gulbahar et al., 2002; Barrs et al., 2005).

# **Clinical Findings**

Mycoplasma spp. infection should be considered a potential differential diagnosis for cats presented for evaluation of conjunctivitis, keratitis, sneezing and mucopurulent nasal discharge, coughing, dyspnea, fever, lameness with or without swollen painful joints, subcutaneous abscessation, or abortion. Mycoplasma spp. or Ureaplasma spp. infections were not associated with lower urinary tract disease of cats in one study (Abou et al., 2006). Mycoplasma spp. or Ureaplasma spp. infection should be considered a potential differential diagnosis for dogs presented for evaluation of coughing, dyspnea, fever, pollakiuria, hematuria, azotemia, lameness with or without swollen painful joints, mucopurulent vaginal discharge, or infertility. Mycoplasma spp. and Ureaplasma spp. are generally not recognized cytologically and usually do not grow on aerobic media; infection should be suspected in animals with neutrophilic inflammation without visible bacteria or negative aerobic culture. The index of suspicion for Mycoplasma spp. or Ureaplasma spp. infection is higher if the animal has neutrophilic inflammation and has been poorly responsive to cell wall-inhibiting antibiotics such as penicillins or cephalosporins.

#### Diagnosis

The clinical laboratory and radiographic abnormalities associated with *Mycoplasma* spp. or *Ureaplasma* spp. infections are similar to those induced by other bacterial infections. Neutrophilia and monocytosis are common in dogs with pneumonia; pyuria and proteinuria occur in dogs with urinary tract disease.

Preputial discharges, vaginal discharges, chronic draining wounds, airway washings, and synovial fluid from animals

with *Mycoplasma* spp. or *Ureaplasma* spp. infections have nondegenerate neutrophils as the most common cell type. Dogs with lower respiratory tract disease and pure *Mycoplasma* cultures have alveolar lung patterns that cannot be differentiated from those in dogs with mixed bacterial and *Mycoplasma* cultures. In some dogs and cats with small airway disease evident radiographically, *Mycoplasma* spp. are isolated from the airways in pure culture (Chandler et al., 2002). Joint radiographs of animals with *Mycoplasma*-associated polyarthritis reveal nonerosive changes.

Specimens for Mycoplasma spp. or Ureaplasma spp. culture should be plated immediately or transported to the laboratory in Hayflicks broth medium, Amies medium without charcoal, or modified Stuart bacterial transport medium. Specimens should be shipped on ice packs if the transport time is expected to be less than 24 hours and on dry ice if the transport time is expected to be longer than 24 hours. Most Mycoplasma spp. require special media, but in one report M. canis grew on regular blood agar plates (L'Abee-Lund et al., 2003). Because the organisms are part of the normal flora, culture of the mucous membranes of healthy animals is never indicated. Because Mycoplasma spp. or *Ureaplasma* spp. can be cultured from healthy animals, interpretation of positive culture results in sick animals is difficult. Most laboratories do not report results of antibiotic susceptibility testing. The disease association is strong if Mycoplasma spp. or Ureaplasma spp. are isolated in pure culture from tissues from which isolation is unusual (lower airway, uterus, joints). Response to treatment with drugs with known activity against Mycoplasma spp. or Ureaplasma spp. may help support the diagnosis of disease induced by these agents. PCR assays are now available for detection of mycoplasmal DNA (Johnson et al., 2004; Chalker et al., 2004a; Low et al., 2007) in several diagnostic laboratories, but they have the same diagnostic limitations as culture and positive results do not prove the organism is alive.

#### **Treatment**

Tylosin, erythromycin, clindamycin, lincomycin, tetracyclines, chloramphenicol, aminoglycosides, and fluoroquinolones are effective for treatment of Mycoplasma spp. or Ureaplasma spp. infections (see Chapter 93). Doxycycline administered orally at 5-10 mg/kg q12-24h is generally effective in animals with a competent immune system or without life-threatening disease and is proposed to have the added benefit of being antiinflammatory. In animals with mixed infections with gram-negative organisms, life-threatening disease, or suspected tetracycline-resistant strains, fluoroquinolones or azithromycin are good alternate antibiotic choices. In one cat with mycoplasmal polyarthritis, enrofloxacin therapy, but not doxycycline therapy, eliminated infection. Treatment for 4 to 6 weeks is usually required for lower airway, subcutaneous, or joint infections. Erythromycin administered orally at 20 mg/kg q8-12h or lincomycin administered orally at 22 mg/kg q12h should be used in pregnant animals.

# **Zoonotic Aspects and Prevention**

Although risk of zoonotic transfer is likely minimal, bite wound transmission of Mycoplasma spp. from an infected cat to the hand of a human being has been reported (McCabe et al., 1987). Most Mycoplasma spp. or Ureaplasma spp. infections in dogs and cats are opportunistic and associated with other causes of inflammation; thus they are not likely to be directly contagious from animal to animal. However, M. felis may be transmitted from cat to cat by conjunctival discharges. Mycoplasma spp. appear to have been associated with respiratory tract disease in dogs and cats as primary pathogens and may be spread from animal to animal, as with M. pneumoniae in human beings. Animals with conjunctivitis or respiratory tract disease should be isolated from other animals until clinical signs of disease have resolved (see Chapter 94). Mycoplasma spp. and Ureaplasma spp. are susceptible to routine disinfectants and rapidly die outside the host.

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#### Mycoplasma and Ureaplasma

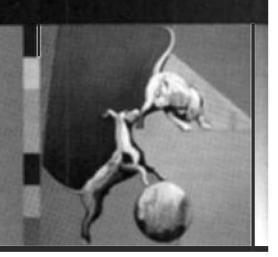
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# CHAPTER

# Polysystemic Rickettsial Diseases



# CHAPTER OUTLINE

CANINE GRANULOCYTOTROPIC ANAPLASMOSIS FELINE GRANULOCYTOTROPIC ANAPLASMOSIS CANINE THROMBOCYTOTROPIC ANAPLASMOSIS CANINE MONOCYTOTROPIC EHRLICHIOSIS FELINE MONOCYTOTROPIC EHRLICHIOSIS CANINE GRANULOCYTOTROPIC EHRLICHIOSIS ROCKY MOUNTAIN SPOTTED FEVER OTHER RICKETTSIAL INFECTIONS

The organisms of the order Rickettsiales, in the families Rickettsiaceae and Anaplasmataceae, were reclassified in 2001 after phylogenetic analyses of the 16S rRNA and groESL gene sequences (Dumler et al., 2001). Some Ehrlichia spp. were transferred to the Neorickettsia genus (including E. risticii) and some Ehrlichia spp., including E. phagocytophila (also called E. equi and human granulocytic Ehrlichia) and E. platys were placed into the genus Anaplasma. The genera Ehrlichia and Neorickettsia were transferred to the family Anaplasmataceae; the genera of Rickettsia and Orientia remained in the Rickettsiaceae. The organisms in Ehrlichia, Anaplasma, and Neorickettsia are classified genetically and by cell tropism (monocytotropic, granulocytotropic, or thrombocytotropic). The organisms of most importance to dogs and cats discussed in this chapter include A. phagocytophilum, A. platys, Ehrlichia canis, E. chaffeensis, E. ewingii, Neorickettsia risticii, Rickettsia rickettsii, and R. felis (Table 96-1).

# CANINE GRANULOCYTOTROPIC ANAPLASMOSIS

# **Etiology and Epidemiology**

Anaplasma phagocytophilum (previously known as E. equi, E. phagocytophila, canine granulocytic Ehrlichia, and human granulocytic ehrlichiosis agent) is known to infect a variety of animals, including small mammals, mountain lions,

coyotes, sheep, cattle, deer, dogs, horses, and human beings (Dumler et al., 2001). Small mammals and deer are natural reservoirs. The distribution of A. phagocytophilum is defined by the range of Ixodes ticks and so is most common in California, Wisconsin, Minnesota, and the northeastern states as well as other areas of the world with this tick genus, including Europe, Asia, and Africa. Birds may play a role in spreading infected ticks and may also serve as a reservoir. In endemic areas, seroprevalence can be quite high; in one study of healthy dogs in California, 47.3% of the dogs tested in one county were seropositive (Foley et al., 2001). Borrelia burgdorferi is also transmitted by Ixodes ticks, so coinfections can occur (Jaderlund et al., 2007). The vector must be attached for approximately 24 to 48 hours to transmit the agent. Clinical signs usually develop approximately 1 to 2 weeks after infection. Neutrophils (and rarely other leukocytes) phagocytize the organism, and once intracellular A. phagocytophilum prevents phagolysosome fusion. This mechanism allows multiplication within the phagosome, which gives the appearance of morula in neutrophils under light microscopy. The exact pathogenesis of disease is still undetermined, and why some dogs but not others develop clinical signs of disease is unclear.

# **Clinical Features**

A. phagocytophilum infection appears to be primarily an acute disease in dogs. It has been associated most commonly with nonspecific signs of fever, lethargy, and inappetence. Stiffness and lameness consistent with musculoskeletal pain are also common, and A. phagocytophilum has been associated with polyarthritis. Vomiting, diarrhea, difficult breathing, cough, lymphadenopathy, hepatosplenomegaly, and central nervous system signs (seizures and ataxia) have also been reported. Dogs can be chronic subclinical carriers, so exacerbation of disease could occur in some dogs. However, chronic disease syndromes such as those associated with E. canis infection have not been documented. In a recent study of dogs with neurologic diseases in Sweden, serologic evidence of exposure to A. phagocytophilum and B. burgdorferi was common, but neither organism was linked to the presence of neurologic disease (Jaderlund et al., 2007). In one



**TABLE 96-1** 

Ehrlichia spp., Anaplasma spp., Neorickettsia spp., and Rickettsia spp. of Primary Significance to Dogs or Cats

GENUS AND SPECIES	SMALL ANIMAL HOST	CELL TROPISM	PRIMARY VECTOR	PRIMARY CLINICAL SYNDROMES
Anaplasma phagocytophilum*	Dog and cat	Granulocytotropic	lxodes spp.	Fever, polyarthritis
Anaplasma platys	Dog	Thrombocytotropic	Rhipicephalus sanguineus?†	Fever, thrombocytopenia, uveitis
Ehrlichia canis	Dog and cat	Monocytotropic	Rhipicephalus sanguineus	Fever and diverse manifestations
Ehrlichia chaffeensis	Dog	Monocytotropic	Amblyomma americanum, Dermacentor variabilis	Subclinical; unclear in natural infections
Ehrlichia ewingii	Dog	Granulocytotropic	Amblyomma americanum	Polyarthritis, fever, meningitis
Neorickettsia risticii	Dog	Monocytotropic	Unknown in dogs‡	Unclear in natural infections but similar to <i>E. canis</i>
Rickettsia rickettsii	Dog and cat	§	Dermacentor spp., Amblyomma americanum, Rhipicephalus sanguineus	Fever and diverse manifestations
Rickettsia felis	Cat	§	Ctenocephalides felis	Subclinical

<sup>\*</sup> Previously E. equi, E. phagocytophila, and the human granulocytic Ehrlichia agent.

study of valvular endocarditis, all dogs with *Bartonella* spp.– associated disease were also seropositive for *A. phagocyto-philum* (MacDonald et al., 2004). Whether the coinfection potentiated the *Bartonella*-associated disease is unknown.

#### Diagnosis

Morula of A. phagocytophilum are commonly detected in neutrophils of most clinically affected dogs, so infection can be confirmed during performance of a complete blood cell count. Although thrombocytopenia and lymphopenia are common, neutrophil counts are usually normal. Hemolytic anemia and thrombocytopenia were thought to be from A. phagocytophilum infection in one dog in the United Kingdom (Boxfield et al., 2005). Reported biochemical panel and urinalysis abnormalities are mild and nonspecific. The morulae cannot be distinguished from those of E. ewingii, but the geographic range of the infections varies between the organisms; the travel history can help rank the differentials. Serologic test results (immunofluorescence assay [IFA] and enzyme-linked immunosorbent assay [ELISA]) can be used if morulae are not identified. A point of care assay that detects antibodies against A. phagocytophilum is available (SNAP 4Dx, IDEXX, Westbrook, Maine). Antibody assay results can be falsely negative in acute cases, so a convalescent test 2 to 3 weeks later may be required to confirm exposure. This assay also detects antibodies against A. platys. Because A. phagocytophilum infections are limited geographically, this antibody test result is not needed in the majority of the United States. Polymerase chain reaction assays performed on blood collected in ethylenediamine tetraacetic acid can be used to confirm infection and differentiate A. phagocytophilum infection from other infections, but microbial DNA can also be amplified from healthy dogs (Henn et al., 2007). Most dogs infected by A. phagocytophilum have subclinical infections, most infected dogs only have an acute phase, exposure rates in endemic areas are high, and the disease syndromes associated with infection have multiple other causes. Thus antibody test results and polymerase chain reaction (PCR) assay results alone cannot be used to prove clinical disease associated with A. phagocytophilum infection. For example, although A. phagocytophilum is known to cause thrombocytopenia and polyarthritis in some dogs, a recent study failed to show an association between A. phagocytophilum PCR assay or serologic test results in dogs with polyarthritis or thrombocytopenia (Foley et al., 2007).

# **Treatment**

Several antibiotics are effective against A. phagocytophilum in vitro (Maurin et al., 2003). Doxycycline administered at 5-10 mg/kg PO q12-24h for at least 10 days is recommended by most clinicians. Whether a 28-day course of

<sup>†</sup> The vector has not been identified and attempts to transmit by R. sanguineus have failed.

<sup>‡</sup>Horses may be infected by ingestion of *N. risticii*-infected metacercariae of trematodes found in intermediate host such as aquatic insects or snails.

<sup>§</sup> Rickettsia are not classified by cell tropism.

doxycycline therapy as recommended for *E. canis* is needed is unknown (Neer et al., 2002). If tetracyclines are used, 22 mg/kg PO q8h for 2 to 3 weeks is recommended. Most dogs respond to therapy within hours to days of initiating therapy.

# **Zoonotic Aspects and Prevention**

A. phagocytophilum infects people as well as dogs and so is zoonotic. Human infections are most likely acquired by direct tick transmission, but handling infected blood and carcasses can also lead to infection. Care should also be taken when handling ticks. No vaccine for A. phagocytophilum infection is currently available. Infection can be avoided by tick control or prophylactic use of tetracyclines when visiting endemic areas. In one study, application of imidacloprid-permethrin prevented transmission of A. phagocytophilum from naturally infected Ixodes scapularis ticks to dogs (Blackburn et al., 2004). Dogs appear to be susceptible to reinfection, so tick control should be maintained at all times in endemic areas. Dogs used for blood donors that reside in endemic areas should be screened for A. phagocytophilum infections by serology or PCR.

# FELINE GRANULOCYTOTROPIC ANAPLASMOSIS

# **Etiology and Epidemiology**

Cats have shown to be susceptible to A. phagocytophilum infection after experimental inoculation (Lewis et al., 1975; Foley et al., 2003). In naturally exposed cats, DNA of A. phagocytophilum has been amplified from several countries, including Sweden, Denmark, Ireland, and the United States (Bjoersdorff et al., 1999; Shaw et al., 2001; Lappin et al., 2004). Morulae consistent with A. phagocytophilum have been detected cytologically in neutrophils of naturally infected cats in other countries, including Brazil, Kenya, and Italy (Almonsy et al., 1998; Buoro, 1989; Tarello et al., 2005). Cats living in endemic areas are commonly seropositive (Magnarelli et al., 2005; Billeter et al., 2007). As in dogs, A. phagocytophilum is transmitted by Ixodes ticks, so infections of cats are likely to be most common in these areas. Although rodents are commonly infected with A. phagocytophilum, whether ingestion or direct contact with rodents plays a role in A. phagocytophilum infection of cats is currently unknown. Although the pathogenesis of disease associated with A. phagocytophilum in cats is unknown, some cats experimentally inoculated with A, phagocytophilum developed antinuclear antibodies and increased interferon-y mRNA, suggesting that an immune pathogenesis of disease may contribute to the clinical findings (Foley et al., 2003).

# **Clinical Features**

Fever, anorexia, and lethargy were the most common clinical abnormalities. Tachypnea has also been detected. Ticks may or may not currently be infesting infected cats. Overall, clinical signs associated with *A. phagocytophilum* infection in

cats were mild and resolved quickly after initiating tetracycline therapy.

# Diagnosis

Approximately 50% of cats with proven clinical infections induced by A. phagocytophilum have a mild thrombocytopenia (66,000 to 118,000/μL). Neutrophilia with a left shift, lymphocytosis, lymphopenia, and hyperglobulinemia have been detected in some cats. Morulae are less commonly detected than in dogs. The abnormalities resolved quickly after doxycycline treatment was initiated (Bjoersdorff et al., 1999; Lappin et al., 2004). Biochemical and urinalysis abnormalities are unusual. Some commercial laboratories offer serologic testing. Infected cats are negative for antibodies against E. canis, so A. phagocytophilum IFA slides should be used. Approximately 30% of cats with proven clinical infections induced by A. phagocytophilum are seronegative when first assessed serologically, but all proven cases to date have ultimately seroconverted. Some mountain lions with A. phagocytophilum DNA amplified from blood have been serum antibody negative (Foley et al., 1999), so a single negative antibody result in an acutely infected cat does not exclude infection. Therefore cats with suspected anaplasmosis may need convalescent serum samples to prove infection. Alternately, antibody testing could be combined with PCR testing of whole blood in acute cases (Lappin et al., 2004).

#### Therapy

Supportive care should be administered as needed. Several antibiotics have been administered to naturally infected cats, but all cats in two studies became clinically normal within 24 to 48 hours after initiation of tetracycline or doxycycline administration and recurrence was not reported (Bjoersdorff et al., 1999; Lappin et al., 2004). Although clinically normal, two cats were still PCR positive 17 days and 90 days after treatment (of 21 to 30 days' duration), respectively, which suggests that treatment with tetracyclines for 21 to 30 days may be inadequate for eliminating the organism from the body (Lappin et al., 2004).

#### **Zoonotic Aspects and Prevention**

See the section on canine granulocytic anaplasmosis for a discussion of zoonotic aspects. To prevent *A. phagocytophilum* infection in cats, ascaricidal products approved for use on cats should be used. *A. phagocytophilum* can likely be transmitted by blood; therefore cats used as blood donors in endemic areas should be screened for infection by serum antibody tests or PCR assay, and positive cats should be excluded as donors.

# CANINE THROMBOCYTOTROPIC ANAPLASMOSIS

#### **Etiology and Epidemiology**

Anaplasma platys was formerly classified as Ehrlichia platys (Dumler et al., 2001). The organism forms morulae in

circulating platelets and has been called canine infectious cyclic thrombocytopenia. Infected dogs have been detected primarily in the south and southeastern United States, Western Europe, South America, Australia, Africa, and the Middle East. Inclusions morphologically similar to A. platys have been detected in one cat in Brazil, but attempts to transmit the organism from a dog to a cat failed (Harvey, 2006). A tick vector is suspected because A. platys DNA has been amplified from ticks. However, attempts to transmit infection by Rhipicephalus sanguineous have failed. After intravenous inoculation the incubation period is 8 to 15 days. Although cyclic thrombocytopenia and parasitemia can occur at 10- to 14-days intervals, organism numbers and severity of thrombocytopenia may lessen over time. Later in infection thrombocytopenia can be severe, but the organism may not be recognized cytologically or by PCR with blood (Eddlestone et al., 2007). In these experimentally infected dogs microbial DNA could be amplified from bone marrow and splenic aspirates. Anemia and thrombocytopenia in dogs experimentally infected with either A. platys and/or E. canis were more persistent in the coinfected dogs (Gaunt et al., 2007).

# **Clinical Features**

Dogs with A. platys infections in the United States are usually subclinically infected or have mild fever. More severely affected dogs have exhibited fever, uveitis, and clinical evidence of bleeding, including ecchymosis, petechia, epistaxis, melena, gingival bleeding, retinal hemorrhage, and hematoma formation. Coinfection with other tick borne agents such as E. canis is common and may potentiate clinical disease (Kordick et al, 1999; Gaunt et al, 2007).

# Diagnosis

Anemia, thrombocytopenia, and neutrophilic leukocytosis can occur. Morulae may or may not be present within platelets. In endemic areas A. platys infection, alone or in combination with other tick-borne agents, should be suspected in dogs with anemia or thrombocytopenia. Serum antibodies can be detected by IFA. Cross-reactivity with E. canis is thought to be minimal but A. platys antibodies may be detected in serologic assays for A. phagocytophilum. Antibody assay results can be falsely negative in acute cases, so a convalescent test 2 to 3 weeks later may be required to confirm exposure. PCR assays performed on blood collected in ethylenediamine tetraacetic acid (EDTA) can be used to confirm infection and differentiate A. platys infections from other infections and microbial DNA can also be amplified from healthy dogs (Kordick et al., 1999) and can be negative in clinically ill dogs (Eddlestone et al., 2007). Most dogs infected by A. platys have subclinical infections, most infected dogs only have an acute phase, exposure rates in endemic areas are high, and the disease syndromes associated with infection have multiple other causes. Thus antibody test results and PCR assay results alone cannot be used to prove clinical disease associated with A. platys infection.

#### **Treatment**

The doxycycline and tetracycline treatment protocols discussed for A. phagocytophilum infections of dogs should also be effective for A. platys infections. If coinfection with E. canis exists, treatment duration should be at least 4 weeks (Neer et al., 2002).

# **Zoonotic Aspects and Prevention**

The strategies discussed for control of A. phagocytophilum infection of dogs should also be effective for A. platys. No known human health risk exists with A. platys.

# CANINE MONOCYTOTROPIC **EHRLICHIOSIS**

# **Etiology and Epidemiology**

Organisms that are associated with monocytotropic ehrlichiosis in naturally infected dogs include Ehrlichia canis, E. chaffeensis, and Neorickettsia risticii var atypicalis. An individual dog can be infected by more than one ehrlichial agent, and coinfection with other tick-borne pathogens is common (Kordick et al., 1999).

E. canis is the most common of these agents and causes the most severe clinical disease; it is maintained in the environment from passage from ticks to dogs. Rhipicephalus sanguineus and Dermacentor variabilis are the known vectors. The organism is not passed transovarially in the tick, so unexposed ticks must feed on a rickettsemic dog in the acute phase to become infected and perpetuate the disease. Male R. sanguineus can take multiple feedings and can both acquire and transmit E. canis in the absence of female ticks (Bremer et al., 2005). Dogs seropositive for E. canis have been identified in many regions of the world and most of the United States, but the majority of cases occur in areas with high concentrations of R. sanguineus, such as the Southwest and Gulf Coast.

E. chaffeensis is a cause of human mononuclear ehrlichiosis. White-tailed deer, voles, coyotes, and opossums are reservoirs, and Amblyomma americanum, D. variabilis, and some Ixodes ticks are vectors. Infections by E. chaffeensis are detected primarily in the southeastern United States. Clinical manifestations in dogs are currently being detailed (Breitschwerdt et al., 1998; Zhang et al., 2003) and appear to be rare. N. risticii var atypicalis has been detected only in the United States to date and causes similar clinical signs as E. canis (Kokoma et al., 1991). Bats and swallows may be the natural reservoirs of this organism. Trematodes of snails and water insects are thought to be the vectors (Pusterla et al., 2003).

Ehrlichia canis infection causes acute, subclinical, and chronic phases of disease. Infected mononuclear cells marginate in small vessels or migrate into endothelial tissues, inducing vasculitis during the acute phase. The acute phase begins 1 to 3 weeks after infection and lasts 2 to 4 weeks; most immunocompetent dogs survive. The subclinical phase lasts months to years in naturally infected dogs. Although

some dogs clear the organism during the subclinical phase, the organism persists intracellularly in some, leading to the chronic phase of infection. Many of the clinical and clinicopathologic abnormalities that develop during the chronic phase are from immune reactions against the intracellular organism. The variable duration of the subclinical phase of disease explains why *E. canis* infection does not have a distinct seasonal incidence as does Rocky Mountain spotted fever (RMSF). However, acute-phase disease is recognized most frequently in the spring and summer when the tick vectors are most active.

#### **Clinical Features**

Clinical disease from ehrlichial infection can occur in any dog, but its severity varies depending on the organism, host factors, and presence of coinfections. Virulence is thought to vary with different field strains of *E. canis*. Dogs with depressed cell-mediated immunity develop severe disease. However, *E. canis* itself did not cause immunosuppression in young, experimentally infected dogs within the first several months of infection (Hess et al., 2006).

Clinical findings in dogs with E. canis infections vary with the timing of infection (Table 96-2). The clinical manifestations of acute-phase disease are quite similar to those of RMSF as a result of the development of vasculitis. Ticks are most commonly found on dogs during the acute phase of infection. Fever can occur in both clinical phases of infection but is more common in dogs with acute ehrlichiosis. Petechiae or other evidence of bleeding noted during the acute phase is generally caused by a combination of mild thrombocytopenia (consumption or immune-mediated destruction) and vasculitis; thrombocytopenia (consumption, immune-mediated destruction, sequestration, decreased production), vasculitis, and platelet function abnormalities (Brandao et al., 2006) occur in the chronic phase. The thrombocytopenia in the acute phase is generally not severe enough to result in spontaneous bleeding, so bleeding may be primarily from vasculitis and decreased platelet function.

Pale mucous membranes usually only occur in the chronic phase during the development of pancytopenia. Hepatomegaly, splenomegaly, and lymphadenopathy are from chronic immune stimulation (i.e., lymphoreticular hyperplasia) and are detected most frequently in dogs in the chronic phase. Interstitial or alveolar edema secondary to vasculitis or inflammation, pulmonary parenchymal hemorrhage secondary to vasculitis or thrombocytopenia, or secondary infections from neutropenia are mechanisms resulting in dyspnea or cough in some dogs with ehrlichiosis. Polyuria, polydipsia, and proteinuria are reported in some dogs that develop renal insufficiency.

Stiffness, exercise intolerance, and swollen, painful joints occur in some dogs with suppurative polyarthritis. Most dogs with polyarthritis from which the organism has been demonstrated have been infected with *E. ewingii* or *A. phagocytophilum*. Ophthalmic manifestations of disease are common; tortuous retinal vessels, perivascular retinal infiltrates, retinal hemorrhage, anterior uveitis, and exudative



**TABLE 96-2** 

Clinical Abnormalities Associated with Ehrlichia canis Infection in Dogs

STAGE OF	ARMORAALIPIKÉ
INFECTION	ABNORMALITIES
	r
Acute	Fever
	Serous or purulent oculonasal discharge
	Anorexia
	Weight loss
	Dyspnea
	Lymphadenopathy
	Tick infestation often evident
Subclinical	No clinical abnormalities
	Ticks often not present
Chronic	Ticks often not present
	Depression
	Weight loss
	Pale mucous membranes
	Abdominal pain
	Evidence of hemorrhage: epistaxis, retinal
	hemorrhage, etc.
	Lymphadenopathy
	Splenomegaly
	Dyspnea, increased lung sounds,
	interstitial or alveolar lung infiltrates
	Ocular: perivascular retinitis, hyphema,
	retinal detachments, anterior uveitis,
	corneal edema
	Central nervous system: meningeal pain, paresis, cranial nerve deficits, seizures
	Hepatomegaly
	Arrhythmias and pulse deficits
	Polyuria and polydipsia
	Stiffness and swollen, painful joints

retinal detachment occur (Komnenou et al., 2007). Central nervous system signs can include depression, pain, ataxia, paresis, nystagmus, and seizures.

#### Diagnosis

Clinicopathologic and radiographic abnormalities consistent with *E. canis* infection are summarized in Table 96-3. Neutropenia is common during acute-phase vasculitis and after bone marrow suppression in the chronic phase. Chronic immune stimulation causes monocytosis and lymphocytosis; lymphocytes often have cytoplasmic azurophilic granules (i.e., large granular lymphocytes). Regenerative anemia is from blood loss (acute and chronic phases); normocytic, normochromic nonregenerative anemia is from bone marrow suppression or anemia of chronic disease (chronic phase). Thrombocytopenia can occur with either acute or chronic ehrlichiosis but is generally more severe with chronic phase disease. Thrombocytopathies from hyperglobulinemia potentiate bleeding in some dogs with chronic ehrlichiosis. Chronic ehrlichiosis is classically associated with pancytopenia,



**TABLE 96-3** 

Clinicopathologic Abnormalities Associated with *Ehrlichia* canis Infection in Dogs

STAGE OF INFECTION	ABNORMALITIES
Acute	Thrombocytopenia
	Leukopenia followed by
1	neutrophilic leukocytosis and
	monocytosis
1	Morulae
	Low-grade, nonregenerative
	anemia unless hemorrhage
	has occurred
	Variable <i>Ehrlichia</i> titer
	PCR positive
Subclinical	Hyperglobulinemia
	Thrombocytopenia
	Neutropenia
	Lymphocytosis
	Monocytosis Positive <i>Ehrlichia</i> titer
Chronic	PCR positive
Chronic	Monocytosis Lymphocytosis
	Thrombocytopenia
	Nonregenerative anemia
	Hyperglobulinemia
	Hypocellular bone marrow
	Bone marrow/spleen
	plasmacytosis
	Hypoalbuminemia
	Proteinuria
	Polyclonal or immunoglobulin G
	monoclonal gammopathy
	Cerebrospinal fluid
	mononuclear cell pleocytosis
	Nonseptic, suppurative
	polyarthritis
	Rare azotemia
	Increased alanine
	aminotransferase and alkaline
	phosphatase activities
	Positive Ehrlichia titer
	PCR positive

PCR, Polymerase chain reaction.

but any combination of neutropenia, thrombocytopenia, and anemia can occur. Changes in bone marrow cell lines associated with ehrlichiosis vary from hypercellular (acute phase) to hypocellular (chronic phase). Bone marrow plasmacytosis is common in dogs with subclinical and chronic ehrlichiosis, and the disease can be confused with multiple myeloma, particularly in dogs with monoclonal gammopathies. Dogs with ehrlichiosis are usually not hypercalcemic and do not have lytic bone lesions.

Hypoalbuminemia in the acute phase is probably caused by third spacing of albumin in tissues because of vasculitis, whereas in chronic-phase disease it is caused by glomerular loss from immune complex deposition or chronic immunostimulation (i.e., monoclonal or polyclonal gammopathy). Prerenal azotemia can occur with acute or chronic disease; renal azotemia develops in some dogs with severe glomerulonephritis from chronic ehrlichiosis. The combination of hyperglobulinemia and hypoalbuminemia is consistent with subclinical or chronic ehrlichiosis. Polyclonal gammopathies are most common, but monoclonal (e.g., immunoglobulin G) gammopathies can also occur.

Aspirates of enlarged lymph nodes and spleen reveal reactive lymphoreticular and plasma cell hyperplasia. Nondegenerate neutrophils are the primary cells in synovial fluid from dogs with polyarthritis caused by any Ehrlichia spp.; E. ewingii and A. phagocytophilum morulae can be identified in synovial neutrophils from some dogs. Bone marrow aspirates in dogs with chronic ehrlichiosis typically reveal myeloid, erythroid, and megakaryocytic hypoplasia in association with lymphoid and plasma cell hyperplasia. Morulae from E. canis are rarely detected in the cytoplasm of mononuclear cells. Ehrlichiosis generally causes mononuclear pleocytosis and increased protein concentrations in cerebrospinal fluid. Antiplatelet antibodies, antinuclear antibodies, antierythrocyte antibodies (by direct Coombs test), and rheumatoid factors are detected in some dogs with ehrlichiosis, leading to an inappropriate diagnosis of primary immune-mediated disease (Smith et al, 2004).

No pathognomonic radiographic signs appear in dogs with ehrlichiosis. The polyarthritis is noncrosive, and dogs with respiratory signs most commonly have increased pulmonary interstitial markings, but alveolar patterns can occur.

Identification of morulae in cells documents *Ehrlichia* infection, but it is uncommon with monocytotropic strains. Examination of buffy coat smears or blood smears made from blood collected from an ear margin vessel may increase the chances of finding morulae. Some *Ehrlichia* spp. can be cultured, but the procedure is low yield and expensive and so is not clinically useful.

Most commercial laboratories (using IFAs) and one point-of-care diagnostic test (SNAP 4Dx) use reagents that detect antibodies against *E. canis* in serum. These tests are generally used as the first screening procedures in dogs suspected to have ehrlichiosis. The American College of Veterinary Internal Medicine (ACVIM) Infectious Disease Study Group suggests that *E. canis* IFA antibody titers between 1:10 and 1:80 be rechecked in 2 to 3 weeks because of the potential for false-positive results at these titer levels (Neer et al., 2002). At low titers, agreement between IFA and ELISA can be poor (O'Connor et al., 2006).

If serum antibodies against *E. canis* are detected in a dog with clinical findings consistent with ehrlichiosis, a presumptive diagnosis of canine ehrlichiosis infection should be made and appropriate treatment begun. However, detection of antibodies alone is not diagnostic of ehrlichiosis because of the existence of cross-reactive antibodies among *E. canis*, *N. helminthoeca*, and *Cowdria ruminantium* and because some dogs are subclinically infected. In addition, negative

test results do not totally exclude ehrlichiosis from the list of differential diagnoses because clinical disease can be detected before seroconversion and not all *Ehrlichia* spp. induce antibodies that are consistently detected in *E. canis* assays.

PCR assays are now available commercially and can be used to detect organism-specific DNA in peripheral blood. It can be performed on joint fluid, aqueous humor, cerebrospinal fluid, and tissues. Blood PCR results can be positive before seroconversion in some experimentally inoculated dogs and positive results document infection, whereas positive serologic tests only document exposure. However, as for serology, no standardization among laboratories currently exists, and insufficient quality control can lead to falsepositive or false-negative results. Until more information is available, the ACVIM Infectious Disease Study Group suggests using PCR with serology, not in lieu of it. Because antibiotic treatment rapidly induces negative blood PCR results, the clinician should draw the blood sample for testing and place it in an EDTA tube before treatment. In one recent study tissues (lymph nodes, spleen, liver, bone marrow, and blood) from naturally infected dogs were assayed by PCR. Blood and lymph nodes were the most likely to be positive but were falsely negative in approximately 30% of the samples (Gal et al., 2007).

#### **Treatment**

Supportive care should be provided as indicated. Several different tetracycline, doxycycline, chloramphenicol, and imidocarb diproprionate protocols have been used. The ACVIM Infectious Disease Study Group currently recommends doxycycline (10 mg/kg PO q24h for at least 28 days). In one study of experimentally infected dogs, ticks still could acquire E. canis from feeding on dogs previously treated with doxycycline for 14 days (Schaefer et al., 2007). Clinical signs and thrombocytopenia should rapidly resolve. If clinical abnormalities are not resolving within 7 days, other differential diagnoses should be considered. Results of studies that used imidocarb diproprionate (5 to 7 mg/kg IM or SQ repeated in 14 days) to treat canine ehrlichiosis have been variable. In one recent study thrombocytopenia persisted and infection was not cleared in experimentally inoculated dogs (Eddlestone et al., 2006). Some patients develop pain at the injection site, salivation, oculonasal discharge, diarrhea, tremors, and dyspnea after administration of this drug. Quinolones are not effective for the treatment of E. canis infections in dogs. Although coinfections common occur, the presence of agents such as A. phagocytophilum, A. platys, and Leishmania infantum did not adversely affect the response to therapy (Mylonakis et al., 2004).

Positive antibody titers have been detected for up to 31 months after therapy in some naturally infected dogs. Dogs with low (less than 1:1024) antibody titers generally revert to negative by 1 year after therapy. Dogs with antibody titers greater than 1:1024 often maintain positive antibody titers after therapy. Whether these dogs are persistent carriers of the organism is undetermined. On the basis of these findings antibody titers are considered to be ineffective for monitor-

ing response to therapy. The ACVIM Infectious Disease Study Group recommends monitoring resolution of thrombocytopenia and hyperglobulinemia as markers of therapeutic elimination of the organism.

Whether ehrlichial infections are cleared by treatment is currently unknown. If PCR is to be used to monitor treatment, the ACVIM Infectious Disease Study Group recommends the following steps be taken. The PCR test should be repeated 2 weeks after stopping treatment. If still positive, treatment should be reinstituted for 4 weeks and retesting performed. If PCR results are still positive after two treatment cycles, an alternate anti-Ehrlichia drug should be used. If PCR results are negative the test should be repeated in 8 weeks, and if still negative therapeutic elimination is assumed to be likely. In one study PCR assay performed on splenic aspirates was superior to blood PCR to document elimination of infection (Harrus et al., 2004).

Whether to treat seropositive healthy dogs is controversial. Arguments for and against testing or treating healthy dogs were reviewed by the ACVIM Infectious Disease Study Group (Neer et al., 2002). The primary reason to treat a seropositive healthy dog is to try to eliminate infection before development of chronic-phase disease. However, treatment of healthy dogs is controversial for at least six reasons: (1) whether treatment halts progression to the chronic phase is unknown; (2) not all seropositive dogs are infected; (3) not all seropositive dogs progress to the chronic phase; (4) whether treatment eliminates infection is unknown; (5) even if infection is eliminated, reinfection can occur; and (6) treatment of healthy carriers may result in antimicrobial resistance.

Because further data are needed to make definitive recommendations, owners should be given the pros and cons and asked to make treatment decisions.

The prognosis is good for dogs with acute ehrlichiosis, and it is variable to guarded for those with chronic ehrlichiosis. Fever, petechia, vomiting, diarrhea, epistaxis, and thrombocytopenia often resolve within days after initiation of therapy in acute cases. Bone marrow suppression from chronic-phase ehrlichiosis may not respond for weeks to months, if at all. Anabolic steroids and other bone marrow stimulants can be administered but are unlikely to be effective because precursor cells are often lacking. Immunemediated events resulting in the destruction of red blood cells or platelets are likely to occur with ehrlichiosis, leading to the recommendation to administer antiinflammatory or immunosuppressive doses of glucocorticoids to acutely affected animals. Prednisone (2.2 mg/kg PO divided q12h during the first 3 to 4 days after diagnosis) may be beneficial in some cases.

#### Zoonotic Aspects and Prevention

Dogs and human beings are both infected by *E. canis*, *E. ewingii*, and *E. chaffeensis* (Buller et al., 1999). Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play a role in the human disease by bringing vectors into the human

environment. Ticks should be removed and handled with care.

Tick control should be maintained at all times; administration of fipronil was shown to lessen transmission in one study (Davoust et al., 2003). Because E. canis is not passed transovarially in the tick, it can be eliminated in the environment by tick control or by treating all dogs through a generation of ticks. Rhipicephalus can only transmit E. canis for approximately 155 days; if tick control is not feasible tetracycline can be administered (6.6 mg/kg PO daily for 200 days). During this time infected dogs will not infect new ticks and previously infected ticks will lose the ability to transmit the organism. Doxycycline given at 100 mg/dog/day was used successfully as a chemopreventative (Davoust et al., 2005). Dogs used as blood donors should be screened serologically yearly and seropositive dogs should not be used.

# FELINE MONOCYTOTROPIC **EHRLICHIOSIS**

# **Etiology and Epidemiology**

Ehrlichia-like bodies or morulae have been detected in peripheral lymphocytes or monocytes of naturally exposed cats in a number of countries, including the United States, Kenya, France, Brazil, and Thailand (Bouloy et al., 1994; Buoro et al., 1994; Beaufils et al., 1995; Beaufils et al, 1999; Almosny et al, 1998; Jittapalapong, 1993). Two studies of naturally infected cats have amplified DNA consistent with E. canis (Breitschwerdt et al., 2002; Beaufils et al., 2002). Other studies of cats in endemic areas (Florida and Arizona) have failed to amplify Ehrlichia spp. DNA from the blood of cats (Luria et al., 2004; Eberhardt et al., 2006). To our knowledge, only two experimental inoculation studies of cats with monocytotropic Ehrlichia spp. have been performed (Dawson et al., 1988; Lappin and Breitschwerdt, unpublished observations, 2007). Morulae of N. risticii were detected in mononuclear cells from two of six cats inoculated intravenously but not subcutaneously; diarrhea developed in one cat and depression, anorexia, and lymphadenomegaly developed in the other. When cats were inoculated subcutaneously with an E. canis strain (North Carolina State University canine isolate) maintained in cell culture, microbial DNA or antibodies that reacted to E. canis morulae were not detected in an 8-week follow-up period (Lappin and Breitschwerdt, unpublished observations, 2007). These results indicate the E. canis-like DNA amplified from naturally infected cats may be from a different Ehrlichia spp. more infective to cats, not all E. canis stains will infect cats, not all cats are susceptible to infection by E. canis, or subcutaneous inoculation is not an effective method for infecting cats with E. canis.

Sera from cats have been assessed for Ehrlichia spp. antibodies by using IFA or Western immunoblot. However, standardization of methods among laboratories has not been performed, the most appropriate cutoff values have not been determined, and variable serologic cross-reactivity has occurred among Ehrlichia spp., Neorickettsia spp., and Anaplasma spp. Therefore results of serologic studies should be interpreted cautiously. Serum antibodies that react with E. canis morulae have been detected by IFA in cats from multiple states in the United States, France, Italy, and Kenya (Bouloy et al., 1994; Matthewman et al., 1996; Pcavy et al., 1989; Beaufils et al., 1999; Stubbs et al., 2000). Although antibodies have been commonly detected in naturally exposed cats, DNA of Ehrlichia spp. is rarely amplified from blood. When taken together these results suggest that cats are less susceptible to monocytotropic ehrlichial infections than are dogs.

How cats are exposed to monocytotropic ehrlichial agents is currently unknown. Documentation of arthropod exposure in proven cases has been variable. Pathogenesis of disease associated with monocytotropic ehrlichiosis in cats is unknown but is likely to be similar to that for E. canis infection of dogs.

#### **Clinical Features**

All ages of cats have been infected; most cats were domestic short haired, and both males and females have been affected. Anorexia, fever, inappetence, lethargy, weight loss, hyperesthesia or joint pain, pale mucous membranes, splenomegaly, dyspnea, and lymphadenomegaly were the most common historic and physical examination abnormalities. Dyspnea, petechiae, retinal detachments, vitreous hemorrhages, and pale mucous membranes were other reported physical examination abnormalities. Concurrent diseases are rarely reported but have included hemoplasmas (previously Haemobartonella felis), Cryptococcus neoformans, feline leukemia virus and feline immunodeficiency virus infections, and lymphoma.

#### Diagnosis

Anemia is common and usually nonregenerative. Leukopenia; leukocytosis characterized by neutrophilia, lymphocytosis, and monocytosis; and intermittent thrombocytopenia have been reported in some cats. Bone marrow evaluation of cats with cytopenias has revealed primarily hypoplasia of the effected cell line. However, one cat had bone marrow cytologic characteristics consistent with myeloid leukemia (Breitschwerdt et al., 2002). Hyperglobulinemia was reported in multiple cats; protein electrophoresis usually reveals a polyclonal gammopathy. An epidemiologic link has been made between the presence of Ehrlichia spp. antibodies in serum and monoclonal gammopathy (Stubbs et al., 2000). On the basis of the cases reported to date, ehrlichiosis should be considered on the differential list for cats with unexplained leukocytosis, cytopenias, and hyperglobulinemia. Biochemical abnormalities were infrequently reported in cats with suspected monocytotropic ehrlichiosis and were nonspecific. The three cats with E. canis-like DNA in the blood also had antinuclear antibodies, similar to results reported for infected dogs (Breitschwerdt et al., 2002).

Some cats with suspected clinical ehrlichiosis seroreacted to E. canis or N. risticii morulae. Antibodies that seroreact to more than one Ehrlichia spp. are sometimes detected. Some cats with E. canis-like DNA in blood were seronegative

(Breitschwerdt et al., 2002). In contrast, most *A. phagocyto-philum*—infected cats have strongly positive antibody test results. Positive serologic test results occur in both healthy and clinically ill cats, so a diagnosis of clinical ehrlichiosis should not be based on serologic test results alone. A tentative diagnosis of clinical feline ehrlichiosis can be based on the combination of positive serologic test results, clinical signs of disease consistent with *Ehrlichia* infection, exclusion of other causes of the disease syndrome, and response to anti-rickettsial drugs. *Ehrlichia* spp. have been cultured from some cats on monocyte cell cultures. PCR and gene sequencing can also be used to confirm infection and should be considered the tests of choice at this time. However, no standardization for dogs exists among laboratories providing *Ehrlichia* spp. PCR assays.

#### **Treatment**

Clinical improvement after therapy with tetracycline, doxycycline, or imidocarb dipropionate was reported for most cats. However, for some cats a positive response to therapy was a criterion for the diagnosis of ehrlichiosis. The current recommendation of the ACVIM Infectious Disease Study Group is to give doxycycline (10 mg/kg PO q24h for 28 days). For cats with treatment failure or those intolerant of doxycycline, imidocarb diproprionate can be given safely (5 mg/kg IM or SQ twice, 14 days apart). Salivation and pain at the injection site are the common adverse effects, and imidocarb efficacy is in question for the treatment of canine monocytotropic ehrlichiosis (Eddlestone et al., 2007).

# Zoonotic Aspects and Prevention

Although cats and human beings can both be infected by *E. canis*, direct transmission is not known to occur. Care should be taken when removing ticks, and arthropod control should be maintained at all time for cats, particularly if allowed outdoors.

# CANINE GRANULOCYTOTROPIC EHRLICHIOSIS

# Etiology and Epidemiology

Ehrlichia ewingii forms morulae in neutrophils and eosinophils and has been detected in dogs and human beings that reside in the southern and southeastern United States. Although one canine case was reported in New York, A. phagocytophilum is more likely in this region (see sections on canine and feline granulocytotropic anaplasmosis). E. ewingii has been detected in a number of ticks, but A. americanum is the only proven vector to date (Murphy et al., 1998). Deer are infected and serve as a reservoir (Yabsley et al., 2002). The incubation period after tick exposure is approximately 13 days. Pathogenesis of disease is unknown but is likely be to similar to other Ehrlichia spp. In general, clinical signs of E. ewingii infection are less severe that those of E. canis. Concurrent disease or infections may play a significant role in the pathogenesis of E. ewingii infection.

#### **Clinical Features**

Nonspecific signs of *E. ewingii* infection include fever, lethargy, anorexia, depression, and signs consistent with polyarthritis, such as stiffness. Other clinical signs include vomiting, diarrhea, and peripheral edema and neurologic signs such as ataxia, paresis, and vestibular disease. Clinical signs can be mild, self-limited, or inapparent (Goodman et al., 2003). Similar to *R. rickettsii*, acute disease seems to be most common, so *E. ewingii* infection should be highest on the list of differential diagnoses from the spring through autumn when *A. americanum* is most active.

# Diagnosis

Suppurative polyarthritis is most common. Other clinicopathologic findings typically associated with acute E. canis infection (Table 96-3), such as mild to moderate thrombocytopenia and anemia, also occur. Morulae can be detected in neutrophils and eosinophils in peripheral blood and in neutrophils from synovial fluid. However, presence of morulae is transient and so easily missed cytologically. The organism has not been cultured to date, so a specific serologic test is not available. However, because the organism is closely related to E. canis, antibodies against E. ewingii can often be detected in E. canis IFA assays. However, E. ewingii antibodies do not bind to the E. canis peptide used in a point-of-care diagnostic assay in the United States (SNAP 4Dx), so this assay cannot be used to screen dogs for E. canis infection (Daniluk et al., 2007). PCR assays are now used to differentiate between members of the Ehrlichia, Anaplasma, and Neorickettsia genera and should be performed on blood collected in EDTA before administration of antibiotics.

#### **Treatment**

Supportive care should be provided as indicated. The tetracycline, doxycycline, and chloramphenicol protocols recommended for *E. canis* infections are generally effective. The ACVIM Infectious Disease Study Group currently recommends doxycycline (10 mg/kg PO q24h for at least 28 days) for *Ehrlichia* spp. infections of dogs (Neer et al., 2002).

# **Zoonotic Aspects and Prevention**

Dogs and human beings are both infected by *Ehrlichia canis*, *E. ewingii*, and *E. chaffeensis* (Buller et al., 1999). Although people cannot acquire ehrlichiosis from handling an infected dog, dogs may be reservoirs for these agents and may play a role in the human disease by bringing vectors into the human environment. Ticks should be removed and handled with care. Dogs used as blood donors should be screened serologically with *E. canis* IFA tests yearly, and seropositive dogs should not be used.

# **ROCKY MOUNTAIN SPOTTED FEVER**

# **Etiology and Epidemiology**

RMSF is caused by *R. rickettsii*. Other members of the genus also infect dogs in the United States; however, they are not

associated with clinical disease but can induce antibodies that cross-react with R. rickettsii (see Diagnosis below). For example, 17 of 22 canine sera submitted for R. akari (rickettsialpox in human beings) IFA testing cross-reacted serologically with R. rickettsii (Comer et al., 2001). In another study of dogs coinfected with several tick-borne pathogens, infection with an uncharacterized rickettsial agent commonly induced cross-reacting antibodies to R. rickettsii (Kordick et al., 1999). Canine RMSF is recognized predominantly in the southeastern states from April through September when the tick vectors are most active. From 1993 to 1996, 52% of human cases of RMSF were reported from the south Atlantic region (Treadwell et al., 2000). Dermacentor andersoni (American wood tick), Dermacentor variabilis (American dog tick), and A. americanum (Lone Star tick) are the principal vectors, host, and reservoir of R. rickettsii. A reemergence of RMSF in the southwestern states has recently occurred, and R. sanguineous ticks are the vector (Demma et al., 2005, 2006; Nicholson et al., 2006). The organism has also been detected in R. sanguineous in California (Wikswo et al., 2007). Strains of R. rickettsii that infect dogs and human beings are closely related genetically (Kidd et al., 2006). Seroprevalence rates are high in endemic areas. In one study of dogs in the southeastern United States 14.1% and 29.7% of healthy and clinically ill dogs, respectively, had detectable R. rickettsii serum antibody titers (Solano-Gallego et al., 2004).

The organism is maintained in nature in a cycle between ticks and small mammals such as voles, ground squirrels, and chipmunks, and it is transmitted transovarially in ticks, so nymphs and larvae can be infected without feeding. R. rickettsii replicates in endothelial tissues (causing vasculitis) and so can lead to diverse and sometimes severe clinical manifestations of disease as soon as 2 to 3 days after exposure. Antiplatelet antibodies can be detected in many infected dogs, suggesting an immune-mediated component to the thrombocytopenia that is frequently present (Grindem et al., 1999). Although seropositive cats have been detected, whether clinical illness occurs is unclear (Case et al., 2006).

# **Clinical Features**

Any dog not previously exposed to R. rickettsii can develop RMSF. The tick frequently feeds on and leaves the dog before the development of clinical signs. In one study only five of 30 owners knew their dogs had been infested by ticks (Gasser et al., 2001). After infection the majority of dogs are subclinical; some develop acute disease with a clinical course of approximately 14 days. No age or sex predilection exists.

Fever and depression are the most common clinical signs. Interstitial pulmonary disease, dyspnea, and cough occur in some dogs, and gastrointestinal signs occur in some acutely infected dogs. Because the disease is generally acute, lymphadenopathy and splenomegaly are not as common as in dogs with ehrlichiosis. Petechiae, epistaxis, subconjunctival hemorrhage, hyphema, anterior uveitis, iris hemorrhage, retinal petechiae, and retinal edema occur frequently. Cutaneous manifestations can include hyperemia, petechiae, edema, and dermal necrosis. Hemorrhage results from vasculitis, thrombocytopenia from consumption of platelets at sites of vasculitis, thrombocytopenia from immune destruction and, in some dogs, disseminated intravascular coagulation. Central nervous system signs include vestibular lesions (nystagmus, ataxia, head tilt), seizures, paresis, tremors, changes in mentation, and hyperesthesia (Mikszewski et al., 2005). Fatal RMSF is generally secondary to cardiac arrhythmias and shock, pulmonary disease, acute renal failure, or severe central nervous system disease.

# Diagnosis

Clinicopathologic and radiographic abnormalities are common but do not definitively document RMSE Neutrophilic leukocytosis, with or without a left shift and toxic cells, is found in most clinically affected dogs. Platelet counts are variable, but in one study 14 of 30 dogs had less than 75,000 platelets/µL without evidence of disseminated intravascular coagulation (Gasser, 2001). In other dogs hemostatic abnormalities consistent with disseminated intravascular coagulation occur. Anemia occurs in some dogs, primarily from blood loss. Increased activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, as well as hypoalbuminemia from blood loss or third spacing of albumin in tissues secondary to vasculitis, occur frequently. Because R. rickettsii does not result in chronic intracellular infection as does ehrlichiosis, hyperglobulinemia is rare. Renal insufficiency in some dogs causes azotemia and metabolic acidosis. Serum sodium, chloride, and potassium concentrations decrease in many dogs with gastrointestinal tract signs or renal insufficiency. Compared with dogs with chronic ehrlichiosis, chronic proteinuria from glomerulonephritis is rare. Positive direct Coombs test results occur in some dogs.

Nonseptic, suppurative polyarthritis occurs in some dogs. CNS inflammation usually causes increased protein concentrations and neutrophilic pleocytosis in cerebrospinal fluid; some dogs may have mononuclear cell pleocytosis or mixed inflammation. No pathognomonic radiographic abnormalities are associated with RMSF, but both experimentally and naturally infected dogs commonly develop unstructured pulmonary interstitial patterns.

A presumptive diagnosis of canine RMSF can be based on the combination of appropriate clinical, historic, and clinicopathologic evidence of disease; serologic test results; exclusion of other causes of the clinical abnormalities; and response to anti-rickettsial drugs. Documentation of seroconversion or an increasing titer 2 to 3 weeks after initial serologic testing suggests recent infection. Diagnostic criteria used in one study included a fourfold rise in antibody titer or a single titer of greater than 1:1024 if the initial titer was submitted 1 week or more after initial onset of clinical abnormalities (Gasser et al., 2001). Positive serum antibody test results alone do not prove RMSF because subclinical infection is common. In addition, positive serum antibody tests do not document infection by R. rickettsii because infection with nonpathogenic spotted fever group agents can induce cross-reacting antibodies. Demonstration of *R. rickettsii* by inoculating affected tissues or blood into susceptible laboratory animals or by documenting the organism in endothelial cells by using direct fluorescent antibody staining leads to a definitive diagnosis of RMSF but is not clinically practical. PCR can be used to document the presence of rickettsial agents in blood, other fluids, or tissues and document infection. However, some apparently healthy dogs have had *Rickettsia* spp. DNA amplified from blood, so positive PCR assay results may not always correlate to RMSF (Kordick et al., 1999).

#### **Treatment**

Supportive care for gastrointestinal tract fluid and electrolyte losses, renal disease, disseminated intravascular coagulation, and anemia should be provided as indicated. Overzealous fluid therapy may worsen respiratory or central nervous system manifestations of disease if vasculitis is severe.

Tetracycline derivatives, chloramphenicol, and enrofloxacin are the antirickettsial drugs used most frequently. Trovafloxacin and, to a lesser extent, azithromycin were beneficial for treatment of RMSF in experimentally inoculated dogs (Breitschwerdt et al., 1999). Tetracycline (22 mg/kg PO q8h for 14 to 21 days) has been commonly used historically. Doxycycline (5 to 10 mg/kg PO q12h for 14 to 21 days) is an alternative to tetracyclines; gastrointestinal absorption and central nervous system penetration are superior to tetracycline because of increased lipid solubility. Chloramphenicol (22 to 25 mg/kg PO q8h for 14 days) can be used in puppies younger than 5 months to avoid dental staining associated with tetracyclines. Enrofloxacin (3 mg/kg PO q12h for 7 days) is as effective as tetracycline or chloramphenicol. In one study of 30 dogs with RMSF, all dogs survived and no apparent differences in response rate occurred among tetracycline, doxycycline, chloramphenicol, or enrofloxacin (Gasser et al., 2001). Fever, depression, and thrombocytopenia often begin to resolve within 24 to 48 hours after starting therapy. Administration of prednisolone at antiinflammatory or immunosuppressive doses in combination with doxycycline did not potentiate RMSF in experimentally infected dogs. The prognosis for canine RMSF is fair; death occurs in less than 5% of affected dogs.

# **Zoonotic Aspects and Prevention**

Because RMSF has not been reported twice in the same dog, permanent immunity is likely. Infection can be prevented by providing strict tick control. Human beings probably do not acquire *R. rickettsii* from contact with dogs, but dogs may increase human exposure to RMSF by bringing ticks into the human environment. People can also be infected when removing ticks with activated *R. rickettsii* from the dog by hand. Two dogs and the owner all died of RMSF in one study (Elchos and Goddard, 2003). As in dogs, RMSF in people is most commonly recognized from April to September when the tick vectors are most active. Untreated RMSF is fatal in approximately 20% of infected people.

# OTHER RICKETTSIAL INFECTIONS

Rickettsia felis was originally detected in a commercial cat flea (Ctenocephalides felis) colony and has been shown to belong in the spotted fever group. Fever, headache, myalgia, and macular rash in human beings have been attributed to R. felis infection around the world. In addition, one person in Mexico developed neurologic symptoms after R. felis infection, suggesting that the organism may be the cause of severe debilitating disease in some people. The organism has been detected in C. felis, C. canis, and Pulex irritans; these fleas have a worldwide distribution. C. felis is a biologic vector for R. felis; the organism can be transmitted transovarially and transtadially within the flea. Rickettsia felis DNA has been amplified from C. felis collected from cats in the United Kingdom, France, Israel, New Zealand, Australia, Thailand, and the United States (Hawley et al., 2006).

In a recent study in our laboratory we assayed 92 pairs of cat blood and flea extracts from Alabama, Maryland, and Texas by using PCR assays that amplify a region of the citrate synthase gene (gltA) and the outer membrane protein B gene (ompB). Of the 92 pairs, 62 (67.4%) of flea extracts and none of the cat blood samples were positive for R. felis DNA (Hawley et al., 2006). In another study we showed R. felis and R. rickettsii antibody prevalence rates in cats with fever to be 5.6% and 6.6%, respectively, but neither organism was amplified from blood (Bayliss et al., 2007). These results prove that cats are sometimes exposed, but further data are needed to determine significance of diseases associations. Because clinical illness in cats has not been documented, optimal treatment is unknown. However, on the basis of results in dogs, doxycycline or a fluoroquinolone would be logical choices. Prevention in cats and people should include flea control.

Neorickettsia helminthoeca (salmon poisoning) causes enteric signs of disease in dogs from the Pacific Northwest. Coxiella burnetii infection is associated with parturient or aborting cats and is primarily a zoonotic disease (see Chapter 100). H. felis has been reclassified as a Mycoplasma.

# Suggested Readings

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# CANINE GRANULOCYTOTROPIC EHRLICHIOSIS

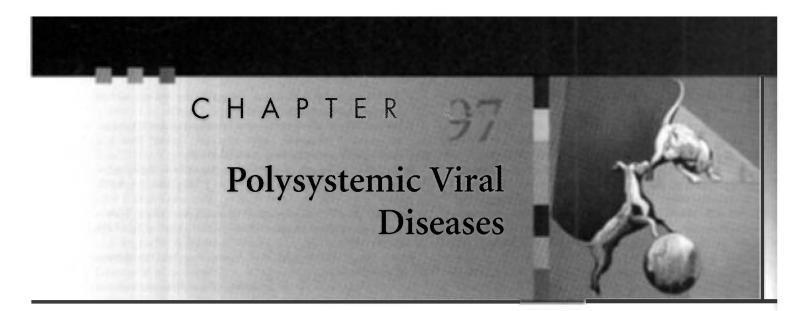
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# CHAPTER OUTLINE

CANINE DISTEMPER VIRUS
FELINE CORONAVIRUS
FELINE IMMUNODEFICIENCY VIRUS
FELINE LEUKEMIA VIRUS

There are multiple viral infections of dogs and cats. Several, including canine distemper virus, some feline coronaviruses, feline leukemia virus, and feline immunodeficiency virus, can cause systemic signs of disease. See other chapters for discussions of viral diseases specific to one organ system.

# **CANINE DISTEMPER VIRUS**

# **Etiology and Epidemiology**

Canine distemper virus (CDV) induces disease predominantly in terrestrial carnivores, but many other species, including seals, ferrets, skunks, badgers, porpoises, and exotic Felidae, have been infected by either CDV or related morbilliviruses. The virus replicates in lymphoid, nervous, and epithelial tissues and is shed in respiratory exudates, feces, saliva, urine, and conjunctival exudates for up to 60 to 90 days after natural infection. After inhalation, the virus is engulfed by macrophages and within 24 hours is carried by lymphatics to tonsillar, pharyngeal, and bronchial lymph nodes, where replication occurs. Central nervous system (CNS) and epithelial tissues are infected approximately 8 to 9 days after initial infection.

The degree of clinical illness and the tissues involved vary depending on the strain of the virus and the immune status of the host (Greene et al., 2006). Nonimmune dogs of any age are susceptible, but the disease is most common in puppies between 3 and 6 months of age. An estimated 25% to 75% of susceptible dogs are subclinically infected after exposure. Massive replication of the virus in the epithelial cells of the respiratory tract, gastrointestinal system, and

genitourinary system occurs in dogs with poor immune responses by postinfection days 9 to 14; these dogs usually die from polysystemic disease. In dogs with moderate immune responses by postinfection days 9 to 14, the virus replicates in epithelial tissues and may result in clinical signs of disease. Dogs with good cell-mediated responses and virus-neutralizing antibody titers by postinfection day 14 clear the virus from most tissues and may not be clinically affected. Most infected dogs develop CNS infection, but clinical signs of CNS disease occur only in dogs with low or no antibody response. Acute demyelination results from restrictive infection of oligodendrogliocytes and subsequent necrosis; chronic demyelination is caused by immune-mediated mechanisms, including antimyelin antibodies and CDV immune complex formation and removal.

#### **Clinical Features**

Many clinically affected dogs are unvaccinated, failed to receive colostrum from an immune bitch, were inappropriately vaccinated, or are immunosuppressed and also have a history of exposure to infected animals. Owners generally present affected dogs for evaluation of depression, malaise, oculonasal discharge, cough, vomiting, diarrhea, or CNS signs. Dogs with poor immune responses generally have the most severe signs and progress rapidly to life-threatening disease. Some partially immune dogs have only mild respiratory disease, presumptively diagnosed as kennel cough syndrome. Tonsillar enlargement, fever, and mucopurulent ocular discharge are common physical examination findings. Increased bronchial sounds, crackles, and wheezes are usually auscultated in dogs with bronchopneumonia.

Hyperesthesia, seizures, cerebellar or vestibular disease, paresis, and chorea myoclonus are common CNS signs that generally develop within 21 days of recovery from systemic disease (Table 97-1). CNS disease is generally progressive and carries a poor prognosis. Some dogs with signs of CNS disease never had systemic signs of disease recognized. Old dog encephalitis is a chronic, progressive panencephalitis in older dogs (older than 6 years) thought to be attributable to CDV infection in which microglial proliferation and neuronal degeneration in the cerebral cortex result in depression,



TABLE 97-1

# Clinical Manifestations of CDV Infection

In utero infection Stillbirth

Abortion

Fading puppy syndrome in the neonatal period

CNS signs at birth

Gastrointestinal tract disease Vomiting

Small-bowel diarrhea

Mucoid to mucopurulent nasal discharge Respiratory tract disease

Sneezing

Coughing with increased bronchovesicular sounds or crackles on auscultation

Dyspnea

Ocular disease Retinochoroiditis, medallion lesions (see Fig. 97-1), optic neuritis

> Keratoconjunctivitis sicca Mucopurulent ocular discharge

Neurologic Disease

Cerebellar disease

Miscellaneous

Spinal cord disease Paresis and ataxia

Head tilt, nystagmus, other cranial nerve and conscious proprioception deficits Central vestibular disease

Ataxia, head bobbing, hypermetria

Generalized or partial seizures ("chewing gum fits") Cerebral disease

Depression

Unilateral or bilateral blindness

Chorea myoclonus Rhythmic jerking of single muscles or muscle groups

> Fever Anorexia

Tonsillar enlargement

Dehydration Pustular dermatosis

Hyperkeratosis of the nose and footpads Enamel hypoplasia in surviving puppies

CDV, Canine distemper virus; CNS, central nervous system.

circling, head pressing, and visual deficits (see Chapter 69 for more information on CNS distemper).

Ocular abnormalities associated with CDV infection include anterior uveitis, optic neuritis with resultant blindness and dilated pupils, and retinochoroiditis. The combination of retinochoroiditis and encephalitis is detected in approximately 40% of affected dogs. Keratoconjunctivitis sicca and hyperreflective retinal scars called medallion lesions occur in some dogs with chronic infection (Fig. 97-1).

Other less-common syndromes have been attributed to CDV infection. Dogs infected before the development of permanent dentition usually have enamel hypoplasia. Hyperkeratosis of the nose and footpads and pustular dermatitis are the most common dermatologic abnormalities. Puppies infected transplacentally can be stillborn, aborted, or born with CNS disease.

#### Diagnosis

The combination of clinical findings and routine clinicopathologic and radiographic evaluation usually leads to a presumptive diagnosis of CDV infection. Lymphopenia and mild thrombocytopenia are consistent hematologic abnormalities. Interstitial and alveolar pulmonary infiltrates are common radiographic findings in dogs with respiratory disease. Although some dogs with CNS infection have normal cerebrospinal fluid (CSF) analyses, most have mononuclear cell pleocytosis and increased protein concentrations. The ratio of serum/CSF immunoglobulin G (IgG) and albumin is commonly high in dogs with encephalitis, but this only documents inflammation of the CNS, not CDV infection.

Measurement of serum or CSF antibody titers can aid in the diagnosis of CDV infection. Documentation of a fourfold increase in the serum IgG titer over a 2- to 3-week period or detection of IgM antibodies in serum is consistent with recent infection or recent vaccination but does not prove clinical disease. CSF antibody titers to CDV are increased in some dogs with encephalitis. False-positive results can occur in CSF samples contaminated with blood. If CSF antibody titers are greater than those in serum, the antibody in the CSF had to be produced locally and is consistent with CNS CDV infection. If increased CSF protein concentrations, mononuclear pleocytosis, and antibodies against CDV are detected in a CSF sample not contaminated with peripheral blood, a presumptive diagnosis of CDV encephalitis can be made.

Definitive diagnosis of CDV infection requires demonstration of viral inclusions by cytologic examination, direct fluorescent antibody staining of cytologic or histopathologic

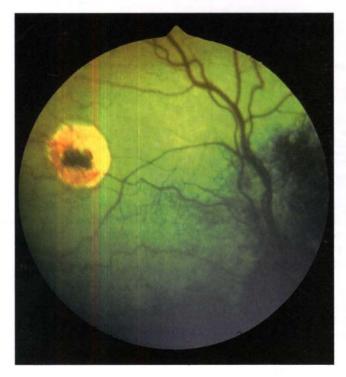


FIG 97-1
Medallion lesions resulting from canine distemper virus infection. (Courtesy Dr. Cynthia Powell, Colorado State University, Fort Collins.)

specimens, histopathologic evaluation, virus isolation, or reverse transcriptase polymerase chain reaction (RT-PCR) documentation of CDV RNA in peripheral blood, CSF, or conjunctival scrapings. Viral inclusions are rarely found in erythrocytes, leukocytes, and leukocyte precursors of infected dogs. Inclusions are generally present for only 2 to 9 days after infection and therefore often are not present when clinical signs occur. Inclusions may be easier to find in smears made from buffy coats or bone marrow aspirates than in those made from peripheral blood. Viral particles can be detected by immunofluorescence in cells from the tonsils, respiratory tree, urinary tract, conjunctival scrapings, and CSF for 5 to 21 days after infection. Recent administration of modified-live CDV-containing vaccines can lead to positive results in direct fluorescent antibody assays and RT-PCR assays. False-positive results have been detected occasionally in direct fluorescent antibody assays performed on conjunctival cells from specific pathogen-free puppies, so results of these tests should be interpreted cautiously (Lappin et al., unpublished data, 2007).

# **Treatment**

Therapy for CDV infection is nonspecific and supportive. Secondary bacterial infections of the gastrointestinal tract and respiratory system are common and, if indicated, should be treated with appropriate antibiotics (see Chapter 93). Anticonvulsants are administered as needed to control seizures (see Chapter 67), but chorea myoclonus has no known

effective treatment. Glucocorticoid administration may be beneficial in some dogs with CNS disease from chronic CDV infection, but it is contraindicated in acutely infected dogs. The prognosis for dogs with CNS distemper is poor.

# **Prevention and Zoonotic Aspects**

The CDV survives in exudates only for approximately 1 hour at body temperature and 3 hours at room temperature and is susceptible to most routine hospital disinfectants. Dogs with gastrointestinal or respiratory signs of disease should be housed in isolation to avoid aerosolization to susceptible populations. Care should be taken to avoid transmission by contaminated fomites (see Chapter 94). All puppies should receive at least three CPV-2, CAV-2, and CDV-containing vaccines, every 3 to 4 weeks, between 6 and 16 weeks of age, with the last booster administered at 14 to 16 weeks of age (see Chapter 94). Modified-live CDV vaccines and the recombinant CDV (rCDV) vaccine are considered adequate by the AAHA Task Force (Paul et al., 2006). Maternal antibodies can block CDV vaccines; therefore in high-risk puppies a modified-live measles virus vaccine has been used between 4 and 12 weeks of age to induce heterologous antibodies that will protect puppies against CDV as maternal antibodies wane. The need for this product is now in question because the rCDV vaccine immunizes puppies in the face of maternal immunity (see Chapter 94). Vaccination against CDV is not as effective if the body temperature is 39.9° C or higher or if other systemic diseases are detected. Vaccines should be boosted at 1 year of age. Recent data suggest that after the 1-year booster, repeat boosters are not needed again for a minimum of 3 years (see Chapter 94).

Disease from CDV infection has occurred in some vaccinated dogs and rarely is attributed to modified-live virus vaccination. Clinical disease in vaccinated dogs develops if the host was immunocompromised, infected with the virus before vaccination, had vaccine-suppressive levels of maternal antibodies, or was incompletely vaccinated. Alternately, the vaccine may have been inactivated by improper handling or may not have protected against all field strains of CDV. Distemper virus encephalitis develops after modified-live vaccination of some dogs coinfected with canine parvovirus; administration of modified-live CDV vaccines should be delayed in dogs with clinical signs of disease consistent with parvovirus infection. Mild, transient thrombocytopenia can be induced by modified CDV vaccination but has not been associated with spontaneous bleeding unless the patient has an underlying subclinical coagulopathy. No proven public health risks are associated with CDV.

# **FELINE CORONAVIRUS**

# **Etiology and Epidemiology**

Coronaviruses causing disease in cats include feline infectious peritonitis (FIP) virus and feline enteric coronavirus (FECV). Enteric infection generally results in mild gastrointestinal signs; systemic infection can induce a clinical syn-

drome with diverse manifestations commonly referred to as FIP. Multiple field strains of FECV and FIP virus have varying degrees of virulence. Mutations or recombinant strains of endemic FECV capable of inducing FIP are believed to develop in the gastrointestinal tract of some infected cats (Vennema et al., 1998).

Enteric coronaviruses are commonly shed in feces and rarely in saliva (Addie et al., 2001) and are highly contagious. Although the prevalence of transplacental transmission is unknown, one epidemiologic study suggested that it is unlikely (Addie et al., 1993). By RT-PCR testing, coronaviruses can be detected in feces as early as 3 days after infection. In studies of FECV-infected, closed cat colonies, almost every cat becomes infected. In one study of 155 pet cats with naturally occurring FECV infection, viral RNA was shed continuously (n = 18) or intermittently (n = 44) in the feces of some cats (Addie et al., 2001). Others were initially shedding viral RNA and then ceased shedding (n = 56), and some were resistant to infection (n = 4). The cats that stopped viral shedding were susceptible to reinfection. Viral RNA was detected in the ileum, colon, and rectum of cats with persistent shedding.

Coronaviruses with the ability to infect monocytes can cause viremia and disseminate throughout the body, potentially resulting in FIP. Between 1986 and 1995, one of every 200 feline accessions at veterinary teaching hospitals in North America was given a clinical diagnosis of FIP (Rohrbach et al., 2001). Most cases of FIP develop in multiple-cat households or catteries. The effusive form of disease develops in cats with poor cell-mediated immune responses; the noneffusive form develops in cats with partial cell-mediated immunity. The effusive form of disease is an immune complex vasculitis characterized by leakage of protein-rich fluid into the pleural space, the peritoneal cavity, the pericardial space, and the subcapsular space of the kidneys. In the noneffusive form pyogranulomatous or granulomatous lesions develop in multiple tissues, particularly the eyes, brain, kidneys, omentum, and liver. Some affected cats have characteristics of both forms of FIP.

Clinical disease associated with FIP virus may be influenced by a number of factors, including the virulence of the strain, the dose of the virus, the route of infection, the immune status of the host, genetically determined host factors, the presence of other concurrent infections, and whether the cat had been previously exposed to a coronavirus. Some breeds appear to be predisposed to the development of FIP (Pesteanu-Somogyi et al., 2006). Feline leukemia virus infection and respiratory tract infection increase the risk for FIP, suggesting that the immune status of the host is important in determining the development of clinical disease. Cats concurrently infected with FIV shed 10 to 100 times more FECV in stool than FIV-naive cats. Experimentally infected, seropositive kittens develop accelerated FIP compared with seronegative kittens when exposed to FIP virus. This antibody-dependent enhancement of virus infectivity occurs because macrophages are more effectively infected by virus complexed with antibody than by virus alone. This phenomenon appears to be rare in naturally infected cats.

#### **Clinical Features**

Enteric replication of coronaviruses commonly results in fever, vomiting, and mucoid diarrhea. With FECV infection clinical signs are self-limiting and generally respond to supportive care within days. Fulminant FIP can occur in cats of any age but is generally recognized in cats younger than 5 years; most cases are younger than 1 year. Intact males are overrepresented in some studies. In cattery outbreaks, usually only one or two kittens in a litter are clinically affected. This may relate to poor transmissibility of strains capable of inducing FIP. Anorexia, weight loss, and general malaise are common presenting complaints (Box 97-1). Icterus, ocular inflammation, abdominal distension, dyspnea, or CNS abnormalities are occasionally noted by the owner.

Fever and weight loss are common with both the effusive and noneffusive forms of the disease. Pale mucous membranes or petechiae are noted in some cats. FIP is one of the most common causes of icterus in cats younger than 2 years; liver size can be normal or enlarged, and the margins are usually irregular. Abdominal distension is common, a fluid wave can often be balloted, and occasionally masses (pyogranulomas or lymphadenopathy) can be palpated in the omentum, mesentery, or intestines. A solitary ileocecocolic or colonic mass, resulting in obstruction leading to vomiting and diarrhea, occurs in some cats. Kidneys can be small (chronic disease) or large (acute disease or subcapsular effusion); renal margins are usually irregular. Pleural effusion can result in dyspnea and a restrictive breathing pattern (shallow and rapid) as well as muffled heart and lung sounds. Male cats sometimes have scrotal enlargement from fluid accumulation.

Anterior uveitis and chorioretinitis occur most frequently with the noneffusive form of the disease and can be its only manifestation. Pyogranulomatous disease can develop anywhere in the CNS, leading to a variety of neurologic signs that include seizures, posterior paresis, and nystagmus.

Feline coronaviruses have been suggested as a cause of failure to conceive, abortion, stillbirth, and congenital defects as well as the fading kitten syndrome (kitten mortality complex). However, one epidemiologic study failed to link feline coronavirus with reproductive failure or neonatal kitten death (Addie et al., 1993).

# Diagnosis

Multiple hematologic, serum biochemical, urinalysis, diagnostic imaging, and CSF abnormalities develop in cats with FIP. Several authors have assessed the predictive values of individual and combinations of tests (Hartmann et al., 2003; Sparkes et al., 1994). Other than histopathology, the positive predictive values of tests used to aid in the diagnosis of FIP are less than 100%. A presumptive diagnosis of FIP is usually based on the combination of clinical and clinicopathologic findings.



BOX 97-1

Clinical Findings Suggestive of FIP in Cats

# Signalment and History

Cats <5 years or >10 years of age

Purebred cat

Purchase from a cattery or multiple-cat household

Previous history of a mild, self-limiting gastrointestinal or respiratory disease

Serologic evidence of infection by FeLV

Nonspecific signs of anorexia, weight loss, or depression

Seizures, nystagmus, or ataxia

Acute, fulminant course in cats with effusive disease Chronic, intermittent course in cats with noneffusive disease

#### **Physical Examination**

Fever

Weight loss

Pale mucous membranes with or without petechiae

Dyspnea with a restrictive breathing pattern

Muffled heart or lung sounds

Abdominal distension with a fluid wave with or without scrotal swelling

Abdominal mass from focal intestinal granuloma or lymphadenopathy

lcterus with or without hepatomegaly

Chorioretinitis or iridocyclitis

Multifocal neurologic abnormalities

Irregularly marginated kidneys with or without renomegaly Splenomegaly

# **Clinicopathologic Abnormalities**

Nonregenerative anemia

Neutrophilic leukocytosis with or without a left shift Lymphopenia

Hyperglobulinemia characterized as a polyclonal gammopathy; rare monoclonal gammopathies

Nonseptic, pyogranulomatous exudate in pleural space, peritoneal cavity, or pericardial space

Increased protein concentrations and neutrophilic pleocytosis in CSF

Positive coronavirus antibody titer in the majority (especially noneffusive)

Pyogranulomatous or granulomatous inflammation in perivascular location on histologic examination of tissues

Positive results of immunofluorescence or RT-PCR performed on pleural or peritoneal exudate

FIP, Feline infectious peritonitis; FeLV, feline leukemia virus; CSF, cerebrospinal fluid; RT-PCR, reverse transcriptase polymerase chain reaction

Normocytic, normochromic, nonregenerative anemia; neutrophilic leukocytosis; and lymphopenia are common. Disseminated intravascular coagulation resulting in thrombocytopenia occurs in some cats. Hyperproteinemia with or without hypoalbuminemia can occur. Polyclonal gammopathies from increases in  $\alpha_2$ -globulin and  $\gamma$ -globulin concentrations are most commonly detected; monoclonal

gammopathies are rare. Most of these findings are consistent with chronic inflammation and do not prove FIP.

Hyperbilirubinemia with variable increases in alanine aminotransferase and alkaline phosphatase activities occurs in some cats with hepatic disease. Prerenal azotemia, renal azotemia, and proteinuria are the most common renal abnormalities. Radiographs can reveal pleural, pericardial, or peritoneal effusions; hepatomegaly; or renomegaly. Mesenteric lymphadenopathy may result in mass lesions in some cats. Ultrasonography can be used to confirm the presence of abdominal fluid in cats with minimal fluid volumes and to evaluate the pancreas, liver, lymph nodes, and kidneys, Magnetic resonance imaging showed periventricular contrast enhancement, ventricular dilation, and hydrocephalus in one group of cats with neurologic FIP (Foley et al., 1998). Protein concentrations and nucleated cell counts (neutrophils predominate in most cases) are commonly increased in CSF from cats with CNS involvement. Although high coronavirus antibody titers are common in the CSF of cats with neurologic FIP, the antibodies appear to be derived from blood and, as the authors of one study concluded, were of equivocal value (Boettcher et al., 2007).

Effusions from cats with FIP are sterile, colorless to straw colored, may contain fibrin strands, and may clot when exposed to air. The protein concentration on fluid analysis commonly ranges from 3.5 g/dL to 12 g/dL and is generally higher than that associated with other diseases. Mixed inflammatory cell populations of lymphocytes, macrophages, and neutrophils occur most commonly; neutrophils predominate in most cases, but in some cats macrophages are the primary cell type seen. In some cats the coronavirus antibody titers are greater in the effusion than in serum. Measurement of protein concentrations in effusions and calculation of the albumin/globulin ratio can aid in the diagnosis of effusive FIP. In one study an albumin/globulin ratio of 0.5 had a positive predictive value of 89%, and an albumin/ globulin ratio of 1.0 had a negative predictive value of 91% (Hartmann et al., 2003). Coronavirus antigens are commonly detected by direct immunofluorescence in the effusions of cats with FIP but not in the effusions of cats with other diseases. In addition, viral RNA can be detected by RT-PCR in effusions and is unlikely to be in effusions from other causes.

Detection of serum antibodies is of limited benefit in the diagnosis of FIP. Infection of cats by any coronavirus can cause cross-reacting antibodies; therefore a positive antibody titer does not diagnose FIP, protect against disease, or predict when a cat may develop clinical FIP. Because coronavirus antibody tests are not standardized, results from different laboratories commonly do not correlate. Cats with FIP are occasionally serologically negative because of rapidly progressive disease, with a delayed rise in titer, disappearance of antibody in terminal stages of the disease, or immune complex formation. Maternal antibodies decline to undetectable concentrations by 4 to 6 weeks of age; kittens infected in the postnatal period become seropositive

at 8 to 14 weeks of age. Thus serologic testing of kittens can be used to prevent the spread of coronaviruses (see below).

Because virus isolation is not practical clinically, RT-PCR is used most frequently to detect coronaviruses in feces. However, positive test results do not differentiate FIP virus from FECV. RNA of both FIP virus and FECV can be amplified from the blood of cats, so positive test results do not always correlate with the development of FIP. Amplification of the mRNA of the M gene by RT-PCR has had mixed results in two studies performed to date (Simons et al., 2005; Can-S Ahna K et al., 2007). In the latter study, 13 of 26 apparently normal cats were positive for FECV mRNA in blood, suggesting that the positive predictive value of this assay for the diagnosis of FIP was low.

Definitive diagnosis of FIP is based on detection of characteristic histopathologic findings, virus isolation, demonstration of the virus in effusions or tissue by use of immunocytochemical or immunohistochemical staining, or demonstration of viral RNA in effusions or tissues by RT-PCR.

#### **Treatment**

Because an antemortem diagnosis of FIP is difficult to make, assessment of studies reporting successful treatment is virtually impossible. A small percentage of cats have spontaneous remission, adding to the confusion concerning therapeutic response. Supportive care, including correction of electrolyte and fluid balance abnormalities, should be provided to cats with FIP as needed.

Optimal treatment of cats with FIP would ideally combine virus elimination with suppression of B-lymphocyte function and stimulation of T-lymphocyte function. In vitro inhibition of FIP virus replication has been demonstrated with a number of drugs, including ribavirin, human interferon-α, feline fibroblastic interferon-β, adenine arabinoside, and amphotericin B. However, to date no uniformly successful antiviral treatment has been developed, and the drugs typically have potentially serious adverse effects.

Because disease from FIP is secondary to immune-mediated reactions against the virus, modulation of the inflammatory reaction is the principal form of palliative therapy. Low-dose prednisolone (1 to 2 mg/kg PO q24h) may lessen clinical manifestations of noneffusive FIP. However, the use of immune-suppressive drugs is controversial because cats with FIP have impaired immune responses (Knotek, 2000). The use of prednisolone and feline interferon has recently been promoted for the treatment of both effusive and noneffusive FIP (Isida et al., 2004). In that study four cats with effusive disease believed to be from FIP virus had prolonged remission. However, the results should be viewed cautiously because the cases were atypical (older cats), the diagnosis of FIP was not confirmed, no control group was used and, if a treatment response occurred, whether it was from the prednisolone or interferon-ywas impossible to determine because both drugs were administered to all cats. Procurement of feline interferon is currently difficult in the United States; whether a positive effect could be achieved by use of human interferons is unknown.

Antibiotics do not have primary antiviral effects but may be indicated for the treatment of secondary bacterial infection. Other supportive care treatments, such as anabolic steroids (stanozolol, 1 mg PO q12h), aspirin (10 mg/kg PO q48-72h), and ascorbic acid (125 mg PO q12h) have also been recommended for the treatment of FIP. Most cats with systemic clinical signs of FIP die or require euthanasia within days to months of diagnosis. The effusive form of disease carries a grave prognosis. Depending on the organ system involved and the severity of polysystemic clinical signs, cats with noneffusive disease have variable survival times. Cats with only ocular FIP may respond to antiinflammatory treatment or enucleation of the affected eye(s) and have a better prognosis than cats with systemic FIP.

# **Prevention and Zoonotic Aspects**

Prevention of coronavirus infections is best accomplished by avoiding exposure to the virus. Although viral particles of FIP can survive in dried secretions for up to 7 weeks, routine disinfectants inactivate the virus. Epidemiologic studies suggest the following:

- · Some healthy, coronavirus-seropositive cats shed the
- Seronegative cats do not usually shed the virus.
- · Kittens are usually not infected by coronaviruses transplacentally.
- · Maternally derived coronavirus antibodies wane by 4 to 6 weeks of age.
- · Kittens are most likely to become infected by contact with cats other than their queens after maternal antibodies wane.
- Coronavirus antibodies from natural infection develop by 8 to 14 weeks of age.

These findings have lead to recommendations that kittens born in a breeding situation with coronavirus-seropositive cats should be housed only with the queen and littermates until sold, should be tested for coronavirus antibodies at 14 to 16 weeks of age, and should be sold only if seronegative. Maintaining a coronavirus-seronegative household and not allowing cats to have contact with other cats would be optimal. Cats can eliminate coronavirus infections; a previously infected cat should be shown to be negative for viral RNA in feces for 5 months and should be seronegative to be considered coronavirus naïve (Addie et al., 2001).

An intranasally administered, mutant strain of coronavirus that induces mucosal immune response but minimal systemic immune response is available (Primucell FIP, Pfizer Animal Health, Exton, Pa.). This strain does not induce FIP; the majority of cats with adverse effects have exhibited only mild signs associated with placement of liquid in the nares, and the vaccine does not appear to potentiate antibodydependent enhancement of virus infectivity when administered to previously seropositive cats (see Chapter 94). The vaccine appears to be effective in at least some cats, but whether the vaccine protects against all field strains, mutations, or recombinants is unknown. The vaccine is not likely to be effective in cats that have previously been infected by a coronavirus. The only indication for the vaccine is for seronegative cats with risk of exposure to coronaviruses, and the American Association of Feline Practitioners considers the vaccine generally not recommended (see Chapter 94). Zoonotic transfer of FIP virus or FECV to human beings has not been documented.

# FELINE IMMUNODEFICIENCY VIRUS

# **Etiology and Epidemiology**

Feline immunodeficiency virus (FIV) is an exogenous, single-strand RNA virus in the family Retroviridae, subfamily Lentivirinae. The virus is morphologically similar to the human immunodeficiency virus (HIV) but it is antigenically distinct. Like FeLV, FIV produces reverse transcriptase to catalyze the insertion of viral RNA into the host genome. Multiple subtypes of the virus exist, and some isolates have differing biologic behavior. For example, immune deficiency is induced much more quickly by some isolates, and clinical diseases, such as uveitis, are induced by some but not all isolates.

Aggressive biting behavior is thought to be the primary route of transmission of FIV; older, male, outdoor cats with clinical signs of disease are most commonly infected. The prevalence of FIV antibodies in North America was 2.5% in a recent study (Levy et al., 2006). FIV is present in semen and can be transmitted by artificial insemination. Transplacental and perinatal transmission occurs from infected queens to kittens. Arthropod transmission appears to be unlikely. Transmission by routes other than biting is less common because high levels of viremia are of short duration. FIV infection of cats has worldwide distribution, and prevalence rates vary greatly by region and the lifestyle of the cats tested. FIV replicates in several cell types, including Tlymphocytes (CD4+ and CD8+), B-lymphocytes, macrophages, and astrocytes. The primary phase of infection occurs as the virus disseminates throughout the body, initially leading to low-grade fever, neutropenia, and generalized reactive lymphadenopathy. A subclinical, latent period of variable length then develops; the length of this period is related in part to the strain of virus and the age of the cat when infected. The median age of healthy, naturally infected cats and clinically ill naturally infected cats is approximately 3 years and 10 years, respectively, suggesting a latent period of years for most strains of FIV. Chronic experimental and naturally occurring infection results in a slow decline in circulating CD4+ lymphocyte numbers, response to mitogens, and decreased production of cytokines associated with cell-mediated immunity, such as interleukin (IL)-2 and IL-10; neutrophil function and natural killer cell function are also affected. Humoral immune responses are often intact, and a polyclonal gammopathy develops from nonspecific

B-lymphocyte activation. Within months to years, an immune deficiency stage similar to acquired immunodeficiency syndrome (AIDS) in human beings develops. Coinfection with FeLV potentiates the primary and immune deficiency phases of FIV. However, coinfection with *Mycoplasma haemofelis*, *Toxoplasma gondii*, feline herpesvirus, and feline calicivirus, as well as immunization, failed to potentiate FIV-associated immunodeficiency.

#### **Clinical Features**

Clinical signs of infection with FIV can arise from direct viral effects or secondary infections that ensue after the development of immunodeficiency (Table 97-2). Most of the clinical syndromes diagnosed in FIV-seropositive cats also occur in FIV-naïve cats, which makes proving disease causation difficult during the subclinical stage of infection. A positive FIV antibody test does not prove immunodeficiency or disease from FIV and does not necessarily indicate a poor prognosis. The only way to determine accurately whether an FIV-seropositive cat with a concurrent infectious disease has a poor prognosis is to treat the concurrent infection.

Primary (acute) FIV infection is characterized by fever and generalized lymphadenopathy. Owners commonly present FIV-infected cats in the immunodeficiency stage for evaluation of nonspecific signs such as anorexia, weight loss, and depression or for evaluation of abnormalities associated with specific organ systems. When a clinical syndrome is diagnosed in a cat seropositive for FIV, the workup should include diagnostic tests for other potential causes (see Table 97-2).

Clinical syndromes reportedly from primary viral effects include chronic small-bowel diarrhea, nonregenerative anemia, thrombocytopenia, neutropenia, lymphadenopathy, pars planitis (inflammation in the anterior vitreous humor), anterior uveitis, glomerulonephritis, renal insufficiency, and hyperglobulinemia. Behavioral abnormalities, with dementia, hiding, rage, inappropriate elimination, and roaming, are the most common neurologic manifestations of FIV infection. Seizures, nystagmus, ataxia, and peripheral nerve abnormalities may occasionally be attributable to primary viral effects. Lymphoid malignancies, myeloproliferative diseases, and several carcinomas and sarcomas have been detected in FIV-infected, FeLV-naïve cats, suggesting a potential association between FIV and malignancy; FIV-infected cats are at higher risk for the development of lymphoma. Although FIV is not oncogenic, it predisposes to neoplasia because of its immunosuppressive effects.

#### Diagnosis

Neutropenia, thrombocytopenia, and nonregenerative anemia are the most common hematologic abnormalities associated with FIV infection. Monocytosis and lymphocytosis occur in some cats and may be caused by the virus or chronic infection with opportunistic pathogens. Cytologic examination of bone marrow aspirates may reveal maturation arrest (i.e., myelodysplasia), lymphoma, or leukemia. A progressive decline in CD4+ lymphocytes, a plateau or pro-

**TABLE 97-2** 

# Clinical Syndromes Associated with FIV Infection and Possible Opportunistic Agents

CLINICAL SYNDROME	PRIMARY VIRAL EFFECT	OPPORTUNISTIC AGENTS		
Dermatologic/otitis externa	None	Bacterial; atypical Mycobacterium; Otodectes cynotis; Demodex cati; Notoedres cati; dermatophytosis; Cryptococcus neoformans; cowpox		
Gastrointestinal	Yes; small-bowel diarrhea	Cryptosporidium spp.; Cystoisospora spp.; Giardia spp.; Salmonella spp.; Campylobacter jejuni; others		
Glomerulonephritis	Yes	Bacterial; FeLV, FIP, SLE		
Hematologic	Yes; nonregenerative anemia; neutropenia; thrombocytopenia	M. haemofelis; FeLV; Bartonella henselae?		
Neoplasia	Yes; myeloproliferative disorders and lymphoma	FeLV		
Neurologic	Yes; behavioral abnormalities	T. gondii; C. neoformans; FIP; FetV, B. henselae?		
Ocular	Yes; pars planitis, anterior uveitis	T. gondii; FIP; C. neoformans, FHV-1, B. henselae		
Pneumonia/pneumonitis	None	Bacterial; T. gondii; C. neoformans		
Pyothorax	None	Bacterial		
Renal failure	Yes	Bacterial; FIP; FeLV		
Stomatitis	None	Calicivirus; overgrowth of bacteria flora; candidiasis, B henselae?		
Upper respiratory tract	None	FHV-1; calicivirus; overgrowth of bacterial flora;  Cryptococcus neoformans		
Urinary tract infection	None	Bacterial		

FIV, Feline immunodeficiency virus; FeLV, feline leukemia virus; FIP, feline infectious peritonitis; SLE, systemic lupus erythematosus; FHV-1, feline herpesvirus type 1.

gressive increase in CD8+ lymphocytes, and an inversion of the CD4+/CD8+ ratio occurs in experimentally infected cats over time. A multitude of serum biochemical abnormalities is possible depending on what FIV-associated syndrome is occurring. Renal azotemia and polyclonal gammopathy are the changes most likely to be attributable to direct viral effects. No pathognomonic imaging abnormalities are associated with FIV infection.

Antibodies against FIV are detected in serum in clinical practice most frequently by enzyme-linked immunosorbent assay (ELISA). Comparisons between different tests have shown the results of most assays are comparable (Hartmann et al., 2007). Clinical signs can occur before seroconversion in some cats and some infected cats never seroconvert; thus false-negative reactions can occur. Results of virus isolation or PCR on blood are positive in some antibody-negative cats. False-positive reactions are common with ELISA; therefore positive ELISA results in healthy or low-risk cats should be confirmed by Western blot immunoassay or RT-PCR. Kittens can have detectable, colostrum-derived antibodies for several months. Kittens younger than 6 months that are FIV seropositive should be tested every 60 days until the result is negative. If antibodies persist at 6 months of age, the kitten is likely infected. Virus isolation or PCR on blood can also be performed to confirm infection. The biggest problem with FIV RT-PCR assays to date is lack of standardization among laboratories and the potential for both false-positive and false-negative results (Crawford et al., 2005). A vaccine against FIV has been licensed in the United States (see

Chapter 94). This vaccine induces antibodies that cannot be distinguished from those induced by naturally occurring disease with currently available tests (see below).

Detection of antibodies against FIV in the serum of cats that have not been vaccinated against FIV documents exposure and correlates well with persistent infection but does not correlate with disease induced by the virus. Because many clinical syndromes associated with FIV can be caused by opportunistic infections, further diagnostic procedures may determine treatable etiologies (see Table 97-2). For example, some FIV-seropositive cats with uveitis are coinfected by *T. gondii* and often respond to the administration of anti-*Toxoplasma* drugs (see Chapter 99).

#### **Treatment**

Because FIV-seropositive cats are not necessarily immunosuppressed or diseased from FIV, the cat should be evaluated and treated for other potential causes of the clinical syndrome. Some FIV-seropositive cats are immunodeficient; if infectious diseases are identified, bacteriocidal drugs administered at the upper end of the dosage should be chosen. Long-term antibiotic therapy or multiple treatment periods may be required. The only way to determine if an FIVseropositive cat with a concurrent infection has a poor prognosis is to treat the concurrent infection.

A variety of antiviral drugs and immune stimulation therapies have been administered to cats with FIV or FeLV infection (Table 97-3). Administration of interferons has shown promise in some studies. Oral administration of



# Drug Treatment Regimens for Viremic, Clinically Ill Cats with FIV or FeLV Infections

THERAPEUTIC AGENT*	ADMINISTRATION
Acemannan	2 mg/kg intraperitoneal once weekly for 6 weeks
AZT	5 mg/kg PO or SQ q12h; monitor for the development of anemia
Bovine lactoferrin	175 mg PO in milk or VAL syrup, q12-24h for treatment of stomatitis
Erythropoietin	100 U/kg SQ three times weekly and then titrate to effect
Interferon-a*	10 IU/kg PO q24h as long as effective
Interferon-feline	1 million U, SQ, q24h for 5 days in three series starting on days 0, 14, and 60
Staphylococcus A	10 µg/kg intraperitoneal twice weekly for 10 weeks and then monthly
Propionibacterium acnes	0.5 mL IV once or twice weekly to effect

Limited information from controlled studies is available for any of these protocols.

Modified from Hartmann K et al: Treatment of feline leukemia virus infection with 3'-azido-2,3-dideoxythymidine and human alpha-interferon, J Vet Intern Med 16:345, 2002.

AZT, Azidothymidine; FIV, feline immunodeficiency virus; FeLV, feline leukemia virus.

10 IU/kg of human interferon-α led to improved clinical signs and prolonged survival compared with a placebotreated control group in one study (Pedretti et al., 2006). In another study feline recombinant interferon was administered at 106 U/kg/day SQ for 5 days in three series (starting on days 0, 14, and 60) and was shown to improve clinical signs early in the study and prolong survival in treated cats (de Mari et al., 2004). Administration of antiviral agents such as the reverse transcriptase inhibitor azidothymidine (AZT) has had mixed success in the treatment of FIV. Use of AZT at a dosage of 5 mg/kg PO or SQ q12h improved overall quality of life and stomatitis in FIV-infected cats and is believed to aid in the treatment of neurologic signs (Hartmann et al., 1995a, 1995b). Cats treated with AZT should be monitored for the development of anemia. Administration of bovine lactoferrin by mouth was beneficial in the treatment of intractable stomatitis in FIV-seropositive cats (Sato et al., 1996). Removal of all premolar and molar teeth has also been effective for treatment of intractable stomatitis in some FIV-seropositive cats (see Chapter 31). Immunomodulators have not been shown to have reproducible clinical effect, but owners sometimes report positive responses. Human recombinant crythropoietin administration increased red blood cell and white blood cell counts, did not increase viral load, and had no measurable adverse clinical effects in FIV-infected cats compared with placebo (Arai et al., 2000). In contrast, although administration of human recombinant granulocyte-monocyte colony-stimulating factor (GM-CSF) to FIV-infected cats increased white blood cell counts in some treated cats, it also induced fever, anti-GM-CSF antibodies, and increased viral load. GM-CSF therefore appears to be contraindicated for the treatment of FIV in cats.

# **Prevention and Zoonotic Aspects**

Housing cats indoors to avoid fighting and testing new cats before introduction to an FIV-seronegative, multiple-cat household will prevent most cases of FIV. Transmission by fomites is unusual because the virus is not easily transmitted by casual contact, is susceptible to most routine disinfectants, and dies when out of the host after minutes to hours, especially when dried. Cleaning litter boxes and dishes shared by cats with scalding water and detergent inactivates the virus. Cats with potential exposure from fighting should be retested 60 days after the potential exposure. Cats that are FIV infected should be housed indoors at all times to avoid exposing FIV-naïve cats in the environment to the virus and to lessen the affected animal's chance of acquiring opportunistic infections. Kittens queened by FIV-infected cats should not be allowed to nurse to avoid transmission by ingestion of milk. Kittens queened by FIV-infected cats should be shown to be serologically negative at 6 months of age to document failure of lactogenic or transplacental transmission before being sold. A killed vaccine containing immunogens from two FIV isolates was recently licensed for use in the United States (Fel-O-Vax FIV, Fort Dodge Animal Health, Overland Park, Kan). However, the efficacy and safety of the vaccine has not been assessed under field conditions in large numbers of cats, so the American Association of Feline Practitioners considers the vaccine noncore (see Chapter 94). In addition, the vaccine induces antibodies that cannot be distinguished from those induced by natural exposure by currently available tests.

HIV and FIV are morphologically similar but antigenically distinct. Antibodies against FIV have not been documented in the serum of human beings, even after accidental exposure to virus-containing material (Butera et al., 2000). Cats with FIV infection resulting in immunodeficiency may be more likely to spread other zoonotic agents into the human environment; clinically ill, FIV-seropositive cats should therefore undergo a thorough diagnostic evaluation (see Chapter 100).

<sup>\*</sup> Several human interferon-α products are available in the United States.

# FELINE LEUKEMIA VIRUS

# **Etiology and Epidemiology**

Feline leukemia virus (FeLV) is a single-strand RNA virus in the family Retroviridae, subfamily Oncovirinae. The virus produces reverse transcriptase, which catalyzes the reaction, resulting in the formation of a DNA copy (provirus) of FeLV viral RNA in the cytoplasm of infected cells; the provirus is inserted into the host cell genome. On subsequent host cell divisions the provirus serves as a template for new virus particles formed in the cytoplasm and is released across the cell membrane by budding. FeLV is composed of several core and envelope proteins. Envelope protein p15e induces immunosuppression. Core protein p27 is present in the cytoplasm of infected cells, peripheral blood, saliva, and tears of infected cats; detection of p27 is the basis of most FeLV tests. The envelope glycoprotein 70 (gp70) contains the subgroup antigens A, B, or C, which are associated with the infectivity, virulence, and disease caused by individual strains of the virus. Neutralizing antibodies are produced by some cats after exposure to gp70. Antibodies against feline oncornavirus-associated cell membrane antigen (FOCMA) are formed by some cats but are generally not used clinically.

The principal route of infection by FeLV is prolonged contact with infected cat saliva and nasal secretions; grooming or sharing common water or food sources effectively results in infection. Because the organism does not survive in the environment, feces, or urine, fomite and aerosol transmission is unlikely. Transplacental, lactational, and venereal transmission is less important than casual contact. FeLV infection has worldwide distribution; the seroprevalence of infection varies geographically and by the population of cats tested. Infection is most common in outdoor male cats between ages 1 and 6 years. In a recent study (Levy et al., 2006) the prevalence of FeLV antigenemia in cats in North

America was 2.3%. FeLV can be detected in feces of infected fleas for 2 weeks (Vobis et al., 2006). However, the prevalence rates for FeLV vary little across regions of the United States with high and low prevalence rates of fleas, so this is an unlikely route of infection.

The virus replicates first in the oropharynx, followed by dissemination through the body to the bone marrow (Table 97-4). If persistent bone marrow infection occurs, infected white blood cells and platelets leave the bone marrow with ultimate infection of epithelial structures, including salivary and lacrimal glands. Whether infection occurs after natural exposure to FeLV is determined by the virus subtype or strain, the virus dose, the age of the cat when exposed, and the cat's immune responses. Using realtime PCR and antigen ELISA results, four classes of FeLV infection were defined (Torres et al. 2005; Levy et al. 2008). Some FeLV-exposed cats can eliminate the infection (abortive) whereas others progress to clinical illness and persistent viremia (progressive). Other FeLV-exposed cats will develop regressive infection characterized by antigen-negative results and lower transiently positive realtime PCR results. Latent FeLV infections are transiently antigen positive but have persistently positive realtime PCR results. Latent and regressive infections can be potentially activated by the administration of glucocorticoids or other immunosuppressive drugs.

The pathogenesis of various syndromes induced by FeLV is complex but includes induction of lymphoma from activation of oncogenes by the virus or insertion of a provirus into the genome of lymphoid precursors; subgroup C induction of aplastic anemia from increased secretion of tumor necrosis factor-α; immunodeficiency attributable to T-lymphocyte depletion (both CD4+ and CD8+ lymphocytes) or dysfunction; neutropenia; neutrophil function disorders; malignant transformation; and viral induction of bone marrow growth-promoting substances leading to myeloproliferative diseases.



**TABLE 97-4** 

Peripheral Blood Test Results in Different Stages of Progressive FeLV Infection

STAGE	ORGANISM LOCALIZATION	TIMING	IFA	ELISA	PCR
ŀ	Replication in local lymphoid tissues (tonsillar and pharyngeal with oronasal exposure)	2-4 days	-	-	-
11	Dissemination in circulating lymphocytes and monocytes	1-14 days	_	+	+
III	Replication in the spleen, distant lymph nodes, and gut- associated lymphoid tissue	3-12 days	-	+	+
IV	Replication in bone marrow cells and intestinal epithelial crypts	7-21 days	-*	+	+
٧	Peripheral viremia, dissemination by infected bone marrow— derived neutrophils and platelets	14-28 days	+	+	+
VI	Disseminated epithelial cell infection with virus secretion in saliva and tears	Day 28+	+†	+	+

Adapted from Rojko JL et al: Pathogenesis of infection by the feline leukemia virus, J Am Vet Med Assoc 199:1305, 1991, and Wolf, 2000. \*IFA may be positive on bone marrow.

<sup>†</sup> Saliva and tears may be positive.

FeLV, Feline leukemia virus; IFA, immunofluorescent antibody; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; —, negative; +, positive.

# **Clinical Features**

Owners generally present FeLV-infected cats for evaluation of nonspecific signs such as anorexia, weight loss, and depression or abnormalities associated with specific organ systems. Of the FeLV-infected cats evaluated at necropsy, 23% had evidence of neoplasia (96% lymphoma/leukemia); the remainder died from nonneoplastic diseases (Reinacher, 1989). Specific clinical syndromes can result from specific effects of the virus or from opportunistic infections caused by immunosuppression. A positive FeLV test result does not prove disease induced by FeLV. When a clinical syndrome is diagnosed in a FeLV-seropositive cat, the workup should include diagnostic tests for other potential causes. The opportunistic agents discussed for FIV also are common in FeLV-infected cats (see Table 97-2).

Bacterial or calicivirus-induced stomatitis occurs in some FeLV-infected cats as a result of immunosuppression. FeLV infection can result in vomiting or diarrhea from a form of enteritis clinically and histopathologically resembling panleukopenia, from alimentary lymphoma, or from secondary infections attributable to immunosuppression. Icterus in FeLV-infected cats can be prehepatic from immunemediated destruction of red blood cells induced by FeLV or secondary infection by *Mycoplasma haemofelis* or "Candidatus Mycoplasma haemominutum"; hepatic from hepatic lymphoma, hepatic lipidosis, or focal liver necrosis; or posthepatic from alimentary lymphoma. Some FeLV-infected cats with icterus may be concurrently infected by FIP virus or T. gondii.

Clinical signs of rhinitis or pneumonia occur in some FeLV-infected cats as a result of secondary infections. Dyspnea or dysphagia from mediastinal lymphoma occurs in some cats. These cats are generally younger than 3 years and may have decreased cranial chest compliance on palpation as well as muffled heart and lung sounds if pleural effusion is present.

Mediastinal, multicentric, and alimentary lymphomas are the most common neoplasms associated with FeLV; lymphoid hyperplasia also occurs. Alimentary lymphoma most commonly involves the small intestine, mesenteric lymph nodes, kidneys, and liver of older cats; most cats with alimentary lymphoma are FeLV negative. Renal lymphoma can involve one or both kidneys, which are usually enlarged and irregularly marginated on physical examination. Fibrosarcomas occasionally develop in young cats coinfected with FeLV and feline sarcoma virus. Lymphocytic, myelogenous, erythroid, and megakaryocytic leukemia all are reported with FeLV infection; erythroleukemia and myelomonocytic leukemia are the most common. The history and physical examination findings are nonspecific.

Renal failure occurs in some FeLV-infected cats from renal lymphoma or glomerulonephritis. Affected cats are presented for evaluation of polyuria, polydipsia, weight loss, and inappetence during the last stages of disease. Urinary incontinence from sphincter incompetence or detrusor hyperactivity occurs in some cats; small-bladder nocturnal incontinence is reported most frequently. Some FeLV-infected cats are presented for miosis, blepharospasm, or cloudy eyes from ocular lymphoma. Aqueous flare, mass lesions, keratic precipitates, lens luxations, and glaucoma are often found on ocular examination. FeLV does not likely induce uveitis without lymphoma. Neurologic abnormalities associated with FeLV infection include anisocoria, ataxia, weakness, tetraparesis, paraparesis, behavioral changes, and urinary incontinence. Nervous system disease is likely to develop as a result of polyneuropathy or lymphoma. Intraocular and nervous system disease in FeLV-infected cats can occur from infection with other agents, including FIP virus, *Cryptococcus neoformans*, or *T. gondii*.

Abortion, stillbirth, or infertility occurs in some FeLV-infected queens. Kittens infected in utero that survive to birth generally develop accelerated FeLV syndromes or die as part of the kitten mortality complex.

Some FeLV-seropositive cats present for lameness or weakness from neutrophilic polyarthritis attributed to immune complex deposition. Multiple cartilaginous exostoses occur in some cats and may be FeLV related.

# **Diagnosis**

A variety of nonspecific hematologic, biochemical, urinalysis, and radiographic abnormalities occur in FeLV-infected cats. Nonregenerative anemia alone or in combination with decreases in lymphocyte, neutrophil, and platelet counts is common. The presence of increased numbers of circulating nucleated red blood cells or macrocytosis in association with severe nonregenerative anemia occurs frequently; examination of bone marrow often documents a maturation arrest in the erythroid line (erythrodysplasia). Immune-mediated destruction of erythrocytes can be induced by FeLV and occurs in cats coinfected with hemoplasmas; regenerative anemia, microagglutination or macroagglutination of erythrocytes, and a positive result on the direct Coombs test are common in these cats. Neutropenia and thrombocytopenia occur from bone marrow suppression or immune-mediated destruction. FeLV-infected cats with the panleukopenia-like syndrome have gastrointestinal tract signs and neutropenia and are difficult to differentiate from cats with panleukopenia virus infection or salmonellosis. Cats with FeLV-induced panleukopenia-like syndrome usually have anemia and thrombocytopenia, abnormalities rarely associated with panleukopenia virus infection. Azotemia, hyperbilirubinemia, bilirubinuria, and increased activity of liver enzymes are common biochemical abnormalities. Proteinuria occurs in some FeLV-infected cats with glomerulonephritis. Cats with lymphoma have mass lesions radiographically depending on the organ system affected. Mediastinal lymphoma can result in pleural effusion; alimentary lymphoma can cause obstructive intestinal patterns.

Lymphoma can be diagnosed by cytologic or histopathologic evaluation of affected tissues (see Chapters 75 and 80). Because lymphoma can be diagnosed cytologically and treated with chemotherapy, cats with mediastinal masses, lymphadenopathy, renomegaly, hepatomegaly, splenomeg-

aly, or intestinal masses should be evaluated cytologically before surgical intervention. Malignant lymphocytes are also occasionally identified in peripheral blood smears, effusions, and CSF.

Most cats with suspected FeLV infection are screened for FeLV antigens in neutrophils and platelets by immunofluorescent antibody (IFA) testing or in whole blood, plasma, serum, saliva, or tears by ELISA. Serum is the most accurate fluid to assess in ELISA tests. IFA results are not positive until the bone marrow has been infected (see Table 97-4). The results of IFA testing are accurate more than 95% of the time. False-negative reactions may occur when leukopenia or thrombocytopenia prevents evaluation of an adequate number of cells. False-positive reactions can occur if the blood smears submitted for evaluation are too thick. A positive IFA result indicates that the cat is viremic and contagious; approximately 90% of cats with positive IFA results are viremic for life. The rare combination of IFA-positive and ELISA-negative results suggests technique-related artifact. Negative ELISA results correlate well with negative IFA results and an inability to isolate FeLV. Comparisons of different antigen tests have shown the results of most assays to be comparable (Hartmann et al., 2007).

The virus can be detected in serum by ELISA before infection of bone marrow and can therefore be positive in some cats during early progressive stages of infection or during early latent infection even though IFA results are negative. Other possibilities for discordant results (ELISA positive, IFA negative) are false-positive ELISA results or false-negative IFA results. Cats with positive ELISA results and negative IFA results are probably not contagious at that time but should be isolated until retested 4 to 6 weeks later because progression to persistent viremia and epithelial cell infection may be occurring.

ELISA-positive cats that revert to negative have developed latent infections or regressive infection. Virus isolation, IFA performed on bone marrow cells, immunohistochemical staining of tissues for FeLV antigen, and PCR can be used to confirm latent or regressive infection in some cats. Cats with latent or regressive infection are not likely contagious to other cats, but infected queens may pass the virus to kittens during gestation or parturition or by milk. Cats with regressive or latent infection can be immunodeficient and may become viremic (IFA and ELISA positive) after receiving corticosteroids or after extreme stress.

A delay of 1 to 2 weeks generally occurs after the onset of viremia before ELISA tear and saliva test results become positive; therefore these test results can be negative even when results with serum are positive. Antibody titers to FeLV envelope antigens (neutralizing antibody) and against virustransformed tumor cells (FOCMA antibody) are available in some research laboratories, but the diagnostic and prognostic significance of results from these tests is unknown. Realtime PCR assays are more sensitive than conventional PCR for FeLV infections, but validated and standardized assays are not currently available in the United States (Torres et al. 2005).

# Treatment

Several antiviral agents have been proposed for the treatment of FeLV; the reverse transcriptase inhibitor AZT has been studied the most (see Table 97-3). Unfortunately, administration of AZT to persistently viremic cats does not appear to clear viremia in most, and it had minimal benefits for clinically ill cats in a recent study (Hartmann et al., 2002). Interferons have an effect against FeLV in vivo and in vitro (Collado et al., 2007; de Mari et al., 2004). Immunotherapy with drugs such as *Staphylococcus* protein A, *Propionibacterium acnes*, or acemannan (see Table 97-3) improves clinical signs of disease in some cats, but controlled studies are lacking.

Chemotherapy should be administered to cats with FeIV-associated neoplasia (see Chapters 77 and 80). Opportunistic agents should be managed as indicated; the upper dose range and duration of antibiotic therapy are generally required. Supportive therapies such as hematinic agents, vitamin B<sub>12</sub>, folic acid, anabolic steroids, and erythropoietin generally have been unsuccessful in the management of nonregenerative anemia. Blood transfusion is required in many cases. Cats with autoagglutinating hemolytic anemia require immunosuppressive therapy, but this may activate virus replication. The prognosis for persistently viremic cats is guarded; the majority die within 2 to 3 years.

# **Prevention and Zoonotic Aspects**

Avoiding contact with FeLV by housing cats indoors is the best form of prevention. Potential fomites such as water bowls and litter pans should not be shared by seropositive and seronegative cats. Testing and removal of seropositive cats can result in virus-free catteries and multiple-cat households.

Because of variations in challenge study methods and the difficulty of assessing the preventable fraction of a disease with a relatively low infection rate, long subclinical phase, and multiple field strains, the efficacy of individual vaccines continues to be in question (see Chapter 94). Vaccination of cats not previously exposed to FeLV should be considered in cats at high risk (i.e., contact with other cats), but owners should be warned of the potential efficacy of less than 100%. Cats with persistent FeLV viremia do not benefit from vaccination. Vaccination is related to the development of fibrosarcoma in some cats (see Chapter 94). Cats developing these tumors may be genetically predisposed (Banerji et al., 2007).

FeLV-infected cats should be housed indoors to avoid infecting other cats and avoid exposure to opportunistic agents. Flea control should be maintained to avoid exposure to hemoplasmas, and *Bartonella* spp. FeLV-infected cats should not be allowed to hunt or be fed undercooked meats to avoid infection by *T. gondii, Cryptosporidium parvum, Giardia* spp., and other infectious agents carried by transport hosts.

Antigens of FeLV have never been documented in the serum of human beings, suggesting that the zoonotic risk is minimal. However, FeLV-infected cats may be more likely than FeLV-naïve cats to pass other zoonotic agents,

such as C. parvum and Salmonella spp., into the human environment.

# **Suggested Readings**

#### CANINE DISTEMPER VIRUS

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#### FELINE INFECTIOUS PERITONITIS VIRUS

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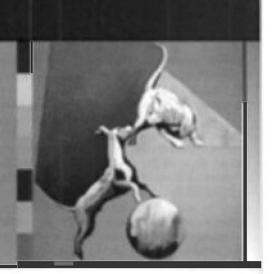
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# CHAPTER

# Polysystemic Mycotic Infections



# CHAPTER OUTLINE

BLASTOMYCOSIS COCCIDIOIDOMYCOSIS CRYPTOCOCCOSIS HISTOPLASMOSIS

# **BLASTOMYCOSIS**

# **Etiology and Epidemiology**

Blastomyces dermatitidis is a saprophytic yeast found primarily in the Mississippi, Missouri, and Ohio River valleys; the mid-Atlantic states; and southern Canada. Two cases in human beings have been reported in Colorado. An extracellular yeast form (5 to 20 pm in diameter) with broad-based budding develops in the vertebrate host (Table 98-1). The infectious mycelial phase occurs in the soil and in culture.

Blastomycosis develops most frequently in areas exposed to high humidity, fog, excavation sites, and sandy, acidic soils near bodies of water. Potential for disease may vary with the virulence of the field strain, the inoculum dose, and the immune status of the host. Most clinical cases occur from point source exposure; multiple cases are diagnosed in an area, and clusters of infection in people and dogs have been reported (MacDonald et al., 2006).

Transmission is from inhalation or contamination of open wounds with spores from the environment. The organism probably replicates in the lungs initially and then spreads hematogenously to other tissues, including the skin and subcutaneous tissues, eyes, bones, lymph nodes, external nares, brain, testes, nasal passages, prostate, liver, mammary glands, vulva, and heart. The organism can be swallowed and passed in feces. Incomplete clearance of the organism by individuals with poor cell-mediated immune responses results in pyogranulomatous inflammation in affected organs, which can cause clinical signs of disease. Subclinical infection is believed to be uncommon in dogs and cats.

# **Clinical Features**

Large-breed, young, male, sporting dogs are infected most commonly by *B. dermatitidis* most likely because of an increased chance for exposure to the organism. Anorexia, cough, dyspnea, exercise intolerance, weight loss, ocular disease, skin disease, depression, lameness, and syncope are the most common presenting complaints.

Fever occurs in approximately 40% of affected dogs. Interstitial lung disease and hilar lymphadenopathy result in cough, dry and harsh lung sounds, and dyspnea; hypertrophic osteopathy occurs in some dogs. Dyspnea from chylothorax caused by cranial vena cava syndrome has been described. Valvular endocarditis occurs as well, and conduction disturbances from myocarditis are detected in some dogs with cardiac blastomycosis (Schmiedt et al., 2006). Lymphadenopathy and cutaneous or subcutaneous nodules, abscesses, plaques, or ulcers occur in 20% to 40% of infected dogs. Splenomegaly is common. Lameness from fungal osteomyelitis of the spine or appendicular skeleton occurs in approximately 30% of dogs with blastomycosis. Infection of the testes, prostate, urinary bladder, and kidneys occurs rarely.

Ocular manifestations are recognized in approximately 30% of dogs with blastomycosis; anterior uveitis, endophthalmitis, posterior segment disease, and optic neuritis occur. Cataracts can result from chronic inflammation or rupture of the lens capsule (Hendrix et al., 2004). Depression and seizures from diffuse or multifocal central nervous system (CNS) involvement occur in some dogs.

Blastomycosis can occur in any cat but is most common in young males. Cats housed indoors and cats allowed outdoors have both been infected (Blondin et al., 2007). Infected cats develop respiratory tract disease, CNS disease, regional lymphadenopathy, dermatologic disease, ocular disease, gastrointestinal tract disease, and urinary tract disease. Pleural or peritoneal effusion resulting in dyspnea or abdominal distension occurs in some cats. Ocular disease usually involves the posterior segment.

#### Diagnosis

Hematologic abnormalities commonly identified in dogs or cats with blastomycosis are normocytic normochromic non-



# **TABLE 98-1**

# Morphologic Appearance of Systemic Canine and Feline Fungal Agents

#### **AGENT** CYTOLOGIC APPEARANCE Extracellular yeast, 5 to 20 .m in diameter; thick, refractile, double-contoured wall; broad-Blastomyces dermatitidis based bud; routine stains are adequate Cryptococcus neoformans Extracellular yeast, 3.5 to 7.0 μm in diameter; thick, unstained capsule; thin-based bud; violet color with light-red capsule with Gram stain; unstained capsule with India ink Coccidiodes immitis Extracellular spherules (20 to 200 µm in diameter) containing endospores; deep red to purple double outer wall with bright red endospores with PAS stain Histoplasma capsulatum Intracellular yeast in mononuclear phagocytes, 2 to 4 µm in diameter, basophilic center with lighter body with Wright's stain Sporothrix schenckii Intracellular yeast in mononuclear phagocytes, 2 to 3 $\mu$ m $\times$ 3 to 6 $\mu$ m in diameter; round, oval, or cigar shaped

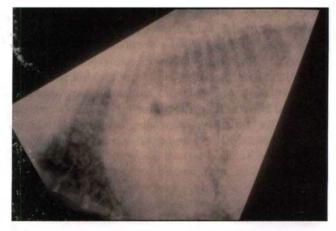


FIG 98-1 Miliary interstitial lung pattern consistent with blastomycosis in a dog. (Courtesy Dr. Lynelle Johnson, College of Veterinary Medicine, University of California, Davis.)

regenerative anemia, lymphopenia, and neutrophilic leukocytosis with or without a left shift and monocytosis. Hypoalbuminemia and hyperglobulinemia (i.e., polyclonal gammopathy) caused by chronic inflammation are common serum biochemical abnormalities; hypercalcemia occurs rarely in dogs. Most infected dogs and cats with respiratory disease have diffuse, miliary, or nodular interstitial lung patterns and intrathoracic lymphadenopathy on thoracic radiographs (Fig. 98-1); single masses and pleural effusion from chylothorax sometimes occur. Alveolar lung disease occurs in some cats (Gilor et al., 2006). Bone lesions induced by blastomycosis are lytic with a secondary periosteal reaction and soft tissue swelling.

Serum antibodies develop in some infected animals. Many cats with blastomycosis are negative for serum antibodies by agar gel immunodiffusion (AGID). False-negative results can occur in animals with peracute infection, immunosuppression, or advanced infection that overwhelms the immune system. Antibody titers do not always revert to

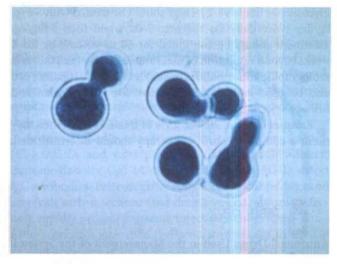


FIG 98-2
Cytologic appearance of the budding yeast, *Blastomyces dermatitidis*. The organism is 5 to 20 µm in diameter with a thick, refractile, double-contoured wall. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

negative after successful treatment. Because blastomycosis rarely causes subclinical infection, positive serologic results combined with appropriate clinical signs and radiographic abnormalities allow presumptive diagnosis if the organism cannot be demonstrated. *Blastomyces* antigens and serum antibodies were detected simultaneously in 36 dogs with confirmed infection (Shurley et al., 2005). However, the assay was not specific for *Blastomyces*. Definitive diagnosis of blastomycosis is based on cytologic, histopathologic, or culture demonstration of the organism (Fig. 98-2). Impression smears from skin lesions and aspirates from enlarged lymph nodes and focal lung lesions usually reveal pyogranulomatous inflammation and organisms that can usually be seen at low power. Recovery of organisms from urine is less consistent. Bronchoalveolar lavage is more sensitive than

transtracheal wash for organism demonstration; organisms can also be found in samples obtained by percutaneous lung aspirates. Growth in culture requires 10 to 14 days and is of lower yield than cytology or biopsy.

# **Treatment**

Amphotericin B, ketoconazole, both amphotericin B and ketoconazole, and itraconazole alone are used most frequently for the treatment of blastomycosis in dogs (Table 98-2). Amphotericin B is generally used in animals with lifethreatening disease; the lipid or liposomal encapsulated product is less likely to cause toxicity. If regular amphotericin B is used, the animal should be well hydrated with 0.9% sodium chloride before treatment, and treatment should be discontinued if the blood urea nitrogen level exceeds 50 mg/ dL. Because itraconazole is as effective as amphotericin B and ketoconazole alone or in combination and has fewer adverse effects, it is the drug of choice for the treatment of blastomycosis (see Table 98-2). Dogs should be treated with 5 mg/ kg/day twice daily for the first 5 days and then 5 mg/kg. Treatment should be continued for 60 to 90 days or for 4 weeks beyond resolution of measurable disease (i.e., thoracic radiographic abnormalities or skin lesions). Fluconazole can also be used and may be effective for CNS, ocular, and urinary system blastomycosis.

Relapses occur in 20% to 25% of treated dogs. When they occur a complete course of therapy should be reinstituted.

Posterior segment ocular disease responds well to itraconazole, but anterior uveitis and endophthalmitis often require enucleation of the affected eye. In dogs with ocular blastomycosis resulting in euthanasia or enucleation of the affected eye, difference in the presence of the organism was not noted between treated and untreated dogs (Hendrix et al., 2004). In one study of 23 cats with blastomycosis, successful results were reported for two cats treated with amphotericin B and ketoconazole, one cat treated with amputation, and one cat treated with potassium iodide (Miller et al., 1990). In a more recent study of eight cats, two cats treated with itraconazole and one cat treated with fluconazole had clinical resolution of their disease (Gilor et al., 2006).

# **Zoonotic Aspects and Prevention**

Direct zoonotic transmission from infected animals is unlikely because the yeast phase is not as infectious as the mycelial phase. One veterinarian was infected after material from a pulmonary aspirate from an infected dog was injected intramuscularly, and another developed disease after being bitten by an infected dog. The mycelial phase develops at temperatures lower than body temperature; positive cultures and contaminated bandages are infectious. Multiple reports have been made of canine and human blastomycosis that developed from the same environment exposure. Decreasing potential for exposure by avoiding lakes and creeks in endemic areas is the only way to prevent the disease.



TABLE 98-2

Antifungal Drugs Used in the Management of the Systemic Canine and Feline Fungal Diseases

DRUG	SPECIES	DOSAGE	ORGANISM
Amphotericin B (regular)	D	0.25 mg/kg, IV as test dose, then 0.5 mg/kg, IV, up to 3 times weekly* 0.5-0.8 mg/kg SQ 2-3 times weekly†	Bl, H, Cr, Co
	С	0.25 mg/kg IV up to 3 times weekly,‡ 0.5-0.8 mg/kg SQ 2-3 times weekly†	Bl, H, Cr, Co
Amphotericin B (liposomal or lipid complex)	В	0.5 mg/kg, IV as test dose, then 1.0 mg/kg, IV, 3-5 times weekly§	Bl, H, Cr, Co
Fluconazole	C	50 mg/cat PO q12-24h	Cr, Bl, H, Co
	D	5 mg/kg PO q12-24h	Bl, H, Cr, Co
Flucytosine¶	В	50 mg/kg PO q8h	Cr
Ketoconazole	В	10 mg/kg PO q12-24h	Bl, H, Cr, Co, Sp
Itraconazole	D	5 mg/kg, PO, g12h for 4 days, then 5-10 mg/kg PO g24h	Bl, Cr, H, Co, Sp
	С	50-100 mg/cat/day PO	Bl, Cr, H, Co, Sp

D, dog; C, cat; B, dog and cat; IV, intravenous; PO, oral; Bl, Blastomyces; H, Histoplasma; Cr, Cryptococcus; Co, Coccidioides; Sp, Sporothrix.

<sup>\*</sup>In dogs with normal renal function, dilute in 60-120 mL 5% dextrose and administer IV over 15 minutes; in dogs with renal insufficiency but with a blood urea nitrogen level <50 mg/dL, dilute in 500 mL to 1 L 5% dextrose and administer IV over 3-6 hours. Cumulative dose of at least 12 mg/kg if used alone or 6 mg/kg if combined with another antifungal drug.

<sup>†</sup> Mix in 400 mL (cats) or 500 mL (dogs) of 0.45% saline and 2.5% dextrose solution and administer SQ.

<sup>‡</sup>In cats with normal renal function, dilute in 50-100 mL 5% dextrose and administer IV over 3-6 hours.

<sup>§</sup> Dilute the contents of a vial with 5% dextrose to a final concentration of 1.0 mg/mL and shake for 30 seconds. Draw up needed volume and filter through an 18-gauge Monoject filter needle into 100 mL of 5% dextrose. Infuse intravenously over 15 minutes.

<sup>¶</sup>Should be used in combination with amphatericin B.

# COCCIDIOIDOMYCOSIS

# **Etiology and Epidemiology**

Coccidioides immitis is a dimorphic fungus found deep in sandy alkaline soils in regions with low elevation, low rainfall, and high environmental temperatures, including the southwestern United States, California, Mexico, Central America, and South America. In the United States coccidioidomycosis is diagnosed most frequently in California, Arizona, New Mexico, Utah, Nevada, and southwest Texas. The environmental mycelial phase produces arthrospores (2 to 4 µm wide, 3 to 10 µm long) that enter the vertebrate host by inhalation or wound contamination. Large numbers of arthrospores return to the surface after periods of rainfall and are dispersed by the wind; the prevalence of coccidioidomycosis increases in the years after a high rainfall. Most cases (67%) of feline coccidioidomycosis are diagnosed between December and May. In one study of dogs residing in an endemic area (Arizona), the cumulative probability of infection (evidenced by scroconversion) by 2 years of age was 28%, and the cumulative probability of clinical infection by 2 years of age was 6% (Shubitz et al., 2005).

Inhaled arthrospores induce neutrophilic inflammation followed by infiltrates of histiocytes, lymphocytes, and plasma cells. Infection is cleared if cell-mediated immune responses are normal; most people, dogs, and cats exposed to the organism are subclinically affected. The organism disseminates to mediastinal and tracheobronchial lymph nodes, bones and joints, visceral organs (liver, spleen, kidneys), heart and pericardium, testicles, eyes, brain, and spinal cord of some individuals. Spherules (20 to 200 µm in diameter) containing endospores (see Table 98-1) form in tissues of infected hosts. Endospores are released by cleavage and produce new spherules. Respiratory signs and signs of disseminated disease occur 1 to 3 weeks and 4 months after exposure, respectively.

# **Clinical Features**

Clinical disease in dogs is most common in young, male, large-breed dogs. Dogs that are allowed to roam or walk in the desert in endemic areas are most likely to be exposed (Butkiewicz et al., 2005). Approximately 90% of clinically affected dogs have lameness with swollen, painful bones or joints. Cough, dyspnea, anorexia, weakness, weight loss, lymphadenopathy, lameness, clinical signs of ocular inflammation, and diarrhea are other presenting complaints. Crackles, wheezes, or muffled lung sounds from pleural effusion are common. Restrictive pericarditis presenting with evidence of right heart failure, such as hepatomegaly, pleural effusion, and ascites, can occur (Heinritz et al., 2005). If subcutaneous abscesses, nodules, ulcers, and draining tracts occur, they are usually associated with infected bones. Myocarditis, icterus, renomegaly, splenomegaly, hepatomegaly, orchitis, epididymitis, keratitis, iritis, granulomatous uveitis, and glaucoma are detected in some dogs. Depression, seizures, ataxia, central vestibular disease, cranial nerve deficits,

and behavioral changes are the most common signs of CNS infection.

The median age of cats with coccidioidomycosis is 5 years; no obvious sex or breed predilection exists. The most common clinical manifestations include skin disease (56%), respiratory disease (25%), musculoskeletal disease (19%), and either ophthalmic or neurologic disease (19%) (Greene et al., 1995).

# Diagnosis

Normocytic, normochromic nonregenerative anemia; leukocytosis; leukopenia; and monocytosis are the most common hematologic abnormalities. Hyperglobulinemia (i.e., polyclonal gammopathy), hypoalbuminemia, renal azotemia, and proteinuria occur in some infected animals (Johnson et al., 2003).

Diffuse interstitial lung patterns are more common than bronchial, miliary interstitial, nodular interstitial, or alveolar patterns radiographically in dogs and cats with respiratory coccidioidomycosis. Pleural effusion from pleuritis, right-sided heart failure, or constrictive pericarditis can occur. Hilar lymphadenopathy is common in dogs and cats; however, sternal lymphadenopathy or calcification of lymph nodes is not. Bone lesions usually involve the distal diaphysis, epiphysis, and metaphysis of one or more long bones, and they are more proliferative than lytic.

Serum antibodies are detected by complement fixation (CF), AGID, and tube precipitin (TP) tests; TP detects immunoglobulin (Ig) M antibodies; CF and AGID detect IgG antibodies. False-negative results can occur in dogs and cats with early infections (less than 2 weeks), chronic infection, rapidly progressive acute infection, and primary cutaneous coccidioidomycosis. False-positive results in the CF test can occur as a result of anticomplementary serum, which may be caused by bacterial contaminants or immune complexes. The assays can cross-react with antibodies against H. capsulatum and B. dermatitidis. Serum antibodies develop in dogs with and without clinical signs of disease, and titer magnitude failed to correlate with the presence of illness in one study (Shubitz et al., 2005). Thus results of antibody test results alone should not be used to make a definitive diagnosis. The combination of positive serologic test results and radiographic signs of interstitial lung disease, dermatologic disease, or osteomyelitis in animals from endemic areas can be used to make a presumptive diagnosis if the organism cannot be demonstrated. Titers may persist for months to years after resolution of clinical disease.

Definitive diagnosis requires demonstration of the organism by cytology, biopsy, or culture. The organism is often difficult to demonstrate by cytology; transtracheal aspiration or bronchoalveolar lavage is commonly negative. Extracellular spherules (Fig. 98-3) are most commonly found in lymph node aspirates, draining masses, and pericardial fluid; wet mount examination of unstained smears or periodic acid—Schiff-stained smears are more suitable than are dry mounts.

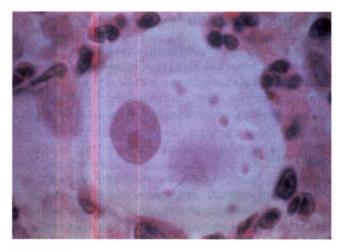


FIG 98-3 Coccidiodes immitis spherule (20 to 200  $\mu$ m in diameter) in muscle tissue.

#### **Treatment**

Ketoconazole is the drug of choice for treatment of coccidioidomycosis in dogs (see Table 98-1), but it commonly leads to inappetence, vomiting, diarrhea, weight loss, and increases in liver enzyme activities in some dogs and cats. In dogs, long-term use of ketoconazole can suppress testosterone and cortisol production and has been associated with cataracts. Amphotericin B should be used if life-threatening disease is present or if response to ketoconazole is poor. Itraconazole can be used in animals with toxicity from ketoconazole.

Fluconazole should be used for animals with meningoencephalitis. Cats and dogs should be treated for 60 to 90 days or until clinical illness has been resolved for at least 1 month. Bone infections are often incurable; therefore repeated treatments are often required. When treated with ketoconazole, itraconazole, or fluconazole, 32 of 44 cats with coccidioidomycosis were asymptomatic during or after treatment (Greene et al., 1995). Relapse occurred in 11 cats during or after treatment. Daily administration of lufenuron, a chitin synthesis inhibitor, has been evaluated in a limited number of dogs with coccidioidomycosis but should not be used in lieu of azoles.

# **Zoonotic Aspects and Prevention**

People exposed to *C. immitis* develop asymptomatic infection or mild, transient respiratory signs. The organism is not transmitted from infected animals to people. However, the mycelial phase occurs outside the vertebrate host, so fomites, such as bandage material and cultures, should be handled carefully. Avoiding endemic areas is the only way to prevent the disease.

# **CRYPTOCOCCOSIS**

# **Etiology and Epidemiology**

Cryptococcus neoformans is a 3.5- to 7.0- m yeastlike organism with worldwide distribution. It has a thick polysaccha-

ride capsule and reproduces by narrow-based budding (see Table 98-1). Cryptococcus neoformans var grubii (serotype A) and C. neoformans var gattii (serotype B) are most commonly associated with disease. Clinical findings with either infection are similar. Many cases have been described in southern California and the eastern coast of Australia. An outbreak of Cryptococcus spp. infections recently occurred in people, dogs, cats, ferrets, and a bird in British Columbia (Lester et al., 2004; MacDougall et al., 2007). Most cases were on Vancouver Island and were caused by C. gattii. The organisms are acquired from the environment; risk factors significantly associated with infection in animals in the British Columbia outbreak included living near a site of soil disturbance such as logging sites, having an above-average level of activity, hunting, and having owners that hiked or visited a botanic garden (Duncan et al., 2006).

The route of transmission for *C. neoformans* is believed to be inhalation. Nasal and pulmonary disease manifestations are common; however, based on culture and serologic studies of healthy animals, an inapparent carrier state also occurs (Malik et al., 1997; Duncan et al., 2005a, 2005b). The organism probably spreads to extrapulmonary sites hematogenously; the CNS may also be infected by direct extension across the cribriform plate from the nasal cavity. Immunity is cell mediated; individuals with incomplete responses do not completely remove the organism, thus resulting in granulomatous lesions. The polysaccharide capsule of the organism inhibits plasma cell function, phagocytosis, leukocyte migration, and opsonization, potentiating infection.

Cryptococcus spp. can be primary pathogens. However, preexisting immunosuppressive conditions are documented in approximately 50% of people with cryptococcosis. Serologic evidence of coinfection with feline immunodeficiency virus or feline leukemia virus occurs in some cats with cryptococcosis. Potentially immunosuppressive conditions such as administration of corticosteroids, ehrlichiosis, heartworm disease, and neoplasia are identified in a small percentage of dogs with cryptococcosis.

# **Clinical Features**

Cryptococcosis is the most common systemic fungal infection of cats and should be considered a differential diagnosis for cats with clinical evidence of upper or lower respiratory tract disease, subcutaneous nodules, lymphadenopathy, intraocular inflammation, fever, or CNS disease. All ages of cats have been infected, but young cats are generally overrepresented. In one study in Australia, Siamese, Himalayan, and Ragdoll breeds were overrepresented (O'Brien et al., 2004). Infection of the nasal cavity, resulting in sneezing and nasal discharge (Fig. 98-4), is reported most frequently. The nasal discharge can be unilateral or bilateral, range from serous to mucopurulent, and often contains blood. Granulomatous lesions extruding from the external nares, facial deformity over the bridge of the nose, and ulcerative lesions on the nasal planum are common. Mandibular lymphadenopathy is detected in most cats with rhinitis. The nasopharynx is the primary site of involvement in some infected cats



FIG 98-4 Severe nasal cryptococcosis in a cat. (Courtesy Dr. Faith Flower, Albuquerque, NM.)

and dogs, resulting in snoring and stertor as the predominant clinical signs. C. gattii has also been detected in pleural effusion (Barrs et al., 2005).

Single or multiple, small (less than 1 cm), cutaneous or subcutaneous masses also have been reported commonly in cats infected with C. neoformans. The masses can be either firm or fluctuant and have a serous discharge if ulcerated. Anterior uveitis, chorioretinitis, or optic neuritis occur in association with ocular infection; lens luxations and glaucoma are common sequelae. Chorioretinitis lesions can be punctate or large; suppurative retinal detachment occurs in some infected cats.

CNS signs of disease result from diffuse or focal meningoencephalitis or focal granuloma formation. Manifestations include depression, behavioral changes, seizures, blindness, circling, ataxia, loss of sense of smell, and paresis depending on the location of the lesion; peripheral vestibular disease can also occur (Beatty et al., 2000). Nonspecific signs of anorexia, weight loss, and fever occur in some infected cats.

Clinical findings in dogs with cryptococcosis depend on the organ systems involved and are similar to those that occur in the cat. Cryptococcosis is diagnosed most commonly in young purebred dogs; Doberman Pinschers, Great Danes, and German Shepherd dogs are commonly affected (Malik et al., 1995; O'Brien et al., 2004). Clinical manifestations include signs of upper or lower respiratory tract infection, disseminated disease including intraabdominal masses, CNS disease, disease of the orbit or eye, skin lesions, nasal cavity disease, and lymph node involvement. Seizures, ataxia, central vestibular syndrome, cranial nerve deficits, and clinical signs of cerebellar disease are the most common CNS manifestations in dogs. Dogs with Cryptococcus

spp.-associated pyelonephritis (Newman et al., 2003) and gastrointestinal disease (Graves et al., 2005) have been reported.

# **Diagnosis**

Nonregenerative anemia and monocytosis are the most common hematologic abnormalities; neutrophil counts and biochemical panels are generally normal. In dogs with CNS involvement, cerebrospinal fluid (CSF) protein concentrations vary from normal to 500 mg/dL, and cell counts vary from normal to 4500/µL; neutrophils and mononuclear cells predominate, but eosinophils are present in some cases. Radiographic changes consistent with cryptococcosis include increased soft tissue density in the nasal cavity caused by fungal granuloma formation as well as nasal bone deformity and lysis. Hilar lymphadenopathy and diffuse to miliary pulmonary interstitial patterns are common thoracic radiographic abnormalities.

Because circulating C. neoformans antibodies can be detected in both healthy and diseased animals, their presence does not document clinical disease. In addition, in one study all infected cats were seronegative (Flatland et al., 1996). Cryptococcal antigen can be detected in serum, aqueous humor, or CSF by latex agglutination (LA); serum antigen tests are positive in most cats and dogs with cryptococcosis. Animals with acute disease, chronic low-grade infections, drug-induced remission, or localized disease can be LA negative. The LA performed on CSF is positive in almost all animals with CNS cryptococcosis. Cryptococcal antigen can also be detected in subclinical carriers (Duncan et al., 2005a, 2005b).

A definitive diagnosis of cryptococcosis is based on positive antigen testing, or cytologic, histopathologic, or culture demonstration of the organism (Fig. 98-5) combined with appropriate clinical manifestations of disease. The organism is found during cytologic evaluation of nasal lesions, cutaneous lesions, lymph node aspirates, CSF, and bronchoalveolar lavage fluid in most affected animals; it can also be cultured. The organism can be cultured from the nasal cavity of some asymptomatic animals, so positive culture results do not always correlate to disease. One study evaluating subclinical carriage of C. gattii showed some animals eliminated the infection, some remained persistently colonized, and some progressed to clinical illness (Duncan et al., 2005a).

#### **Treatment**

Dogs and cats with cryptococcosis have been treated with amphotericin B, ketoconazole, itraconazole, fluconazole, and 5-flucytosine alone and in various combinations (see Table 98-2). Amphotericin B is usually not indicated unless lifethreatening disseminated disease requiring rapid response to therapy is required. If amphotericin B is deemed necessary, lipid or liposomal encapsulated amphotericin is likely optimal because fewer adverse effects are associated with these formulations compared with regular amphotericin B. However, for owners who cannot afford this therapy, a lessexpensive subcutaneous protocol for administration of

FIG 98-5 Cytologic appearance of *Cryptococcus neoformans*. The organism is 3.5 to 7.0  $\mu$ m in diameter and has a thick polysaccharide capsule. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

regular amphotericin B has been used successfully for the treatment of cryptococcosis in dogs and cats and may be effective for other systemic fungi that are susceptible to the drug (Malik et al., 1996a; see Table 98-2).

Ketoconazole, itraconazole, or fluconazole are used as single agents in dogs or cats without life-threatening disease. Ketoconazole commonly leads to inappetence, vomiting, diarrhea, weight loss, and increases in liver enzyme activities in some dogs and cats. In dogs, long-term use of ketoconazole can suppresses testosterone and cortisol production and has been associated with cataracts. Because of these problems, ketoconazole is used less frequently than itraconazole and fluconazole. Fluconazole should be considered for dogs or cats with ocular or CNS infection. If clinical signs of toxicity develop (inappetence; drug eruptions) or increased activity of alanine aminotransferase is detected, drug therapy should be stopped and then reinstituted at 50% of the original dose after signs of toxicity abate.

Flucytosine crosses the blood-brain barrier better than ketoconazole or amphotericin B, so it has been used primarily for the treatment of CNS cryptococcosis. It must be used in combination with other antifungal drugs and has many adverse effects, including vomiting, diarrhea, hepatotoxicity, cutaneous reactions, and bone marrow suppression.

Clinical signs of nasal and cutaneous cryptococcosis generally resolve with treatment, but dogs or cats with CNS or ocular disease are less likely to respond. Treatment should continue for at least 1 to 2 months past resolution of clinical disease. Serum and CSF LA antigen titers can diminish with therapy and have been used to monitor response. Antigen titers fail to decrease in some animals without clinical evi-

dence of disease, suggesting persistence of the organism in tissues.

# **Zoonotic Aspects and Prevention**

People and animals can have the same environmental exposure to *Cryptococcus* spp., but zoonotic transfer from contact with infected animals is unlikely. Prevention is achieved by decreasing potential for exposure.

## HISTOPLASMOSIS

# **Etiology and Epidemiology**

Histoplasma capsulatum is a saprophytic dimorphic fungus found in the soil in all regions with tropical and subtropical climates; histoplasmosis is diagnosed most frequently in the Mississippi, Missouri, and Ohio River valleys and in the mid-Atlantic states. The organism has also been associated with disease in a dog in Australia, a dog in Japan, and two indoor cats in California (Johnson et al., 2004). The microconidia (2 to 4  $\mu m$ ) and macroconidia (5 to 18  $\mu m$ ) of the mycelial phase are found in the environment. In the vertebrate host, the 2- to 4-11m yeast phase is found in the cytoplasm of mononuclear phagocytes (see Fig. 98-6 and Table 98-1).

Histoplasma capsulatum is concentrated most heavily in soil contaminated with bird or bat excrement. Point sources for infection are found in endemic areas; two dogs and 20 people developed pulmonary histoplasmosis after removing a tree that had served as a bird roost (Ward et al., 1979). Subclinical infections are common in dogs. Dogs in endemic areas are commonly exposed but the incidence of disease is low. Immunosuppression may predispose to clinical infection in dogs and cats.

Infection is by ingestion or inhalation of microconidia from the environment. The organism is engulfed by mononuclear phagocytes, transformed to the yeast phase, and transported throughout the body in the blood and lymph. Granulomatous inflammation results in persistently infected organs and clinical signs of disease. Disseminated disease is common in cats.

# **Clinical Features**

Most dogs with histoplasmosis are outdoor sporting breeds younger than 7 years. Subclinical infection, pulmonary infection, and disseminated infection are recognized most frequently. Most affected dogs are presented for evaluation of anorexia, fever, depression, weight loss, cough, dyspnea, or diarrhea. Large-bowel diarrhea is most common, but small-bowel diarrhea, mixed-bowel diarrhea, and protein-losing enteropathy occur in some.

Physical examination abnormalities often include depression, increased bronchovesicular sounds, respiratory wheezes, fever, evidence of diarrhea, pale mucous membranes, hepatomegaly, splenomegaly, icterus, ascites, and intraabdominal lymph node enlargement. Airway obstruction from massive hilar lymphadenopathy occurs in some dogs (Schulman et al., 1999). Lameness from bone infection or polyarthritis,

peripheral lymphadenopathy, chorioretinitis, CNS disease, and skin disease occur occasionally. Subcutaneous nodules rarely drain or ulcerate and are less common than in dogs with cryptococcosis or blastomycosis.

Infected cats are either normal or develop disseminated disease. Most clinically affected cats are younger than 4 years, and some are coinfected with feline leukemia virus. Depression, weight loss, anorexia, lameness, and dyspnea are common presenting complaints. Weight loss can be severe and develop in as little as 2 weeks. Fever (103.5° to 105° F), pale mucous membranes, abnormal lung sounds, oral erosions or ulcers, peripheral or visceral lymphadenopathy, icterus, soft tissue swelling around osseous lesions, hepatomegaly, skin nodules and, rarely, splenomegaly are physical examination abnormalities potentially consistent with histoplasmosis. Disseminated disease has a grave prognosis in cats. Osseous histoplasmosis is most common in bones of the appendicular skeleton distal to the stifle or elbow joints, and one or more limbs can be involved. Feline ocular histoplasmosis manifests with conjunctivitis, chorioretinitis, retinal detachment, or optic neuritis and may induce glaucoma and blindness. Other than depression, CNS signs are uncommon.

# **Diagnosis**

A variety of nonspecific clinicopathologic and radiographic abnormalities are associated with histoplasmosis. Normocytic, normochromic, nonregenerative anemia is the most common hematologic abnormality in both dogs and cats. Neutrophil counts can be normal, increased, or decreased. Unlike the other systemic fungi, *H. capsulatum* is occasionally seen in circulating cells, particularly on examination of a buffy coat smear; mononuclear cell infection is most common, followed by eosinophils. Thrombocytopenia from disseminated intravascular coagulation or microangiopathic destruction occurs in approximately 50% of dogs and some cats. Some affected cats develop pancytopenia from bone marrow infection. Hypoproteinemia and increased activities of alkaline phosphatase and alanine aminotransferase occur in some infected animals.

Lysis predominates in animals with bone infection; periosteal and endosteal new bone production occurs in some cases. In dogs with pulmonary infection, radiographic abnormalities include diffuse interstitial, miliary-to-nodular interstitial disease; hilar lymphadenopathy; pleural effusion; and calcified pulmonary parenchyma caused by chronic disease. In some dogs massive hilar lymphadenopathy is the only radiographic finding. Alveolar lung disease, tracheobronchial lymphadenopathy, and calcified lymph nodes are uncommon in cats. Colonoscopic findings in dogs with gastrointestinal infection include increased mucosal granularity, friability, ulceration, and thickness.

Several tests have been evaluated for the detection of circulating antibodies against *H. capsulatum* in the serum of dogs and cats, but the sensitivity and specificity are poor for all. Serologic diagnosis is unreliable and should be used only to establish a presumptive diagnosis when the organism

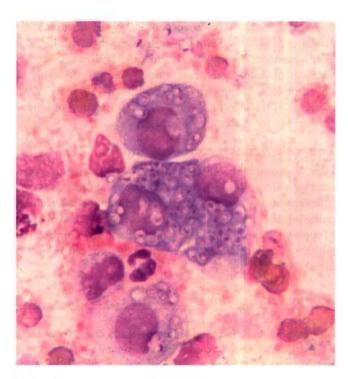


FIG 98-6
Histoplasma capsulatum (2 to 4 μm in diameter) in mononuclear cells. (Courtesy Dr. Dennis Macy, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.)

cannot be demonstrated by cytology, histopathology, or culture and the clinical signs are suggestive of the disease.

Definitive diagnosis requires demonstration of the organism by cytology, biopsy, or culture (Fig. 98-6). The organism is found most frequently in rectal scrapings or biopsies from dogs with large-bowel diarrhea, in bone marrow or buffy coat cells from cats with disseminated disease, and in other locations (e.g., lymph nodes, lung, spleen, liver, skin nodules). The organism has also been identified in pleural and peritoneal effusions and in CSF.

## **Treatment**

Because of its effectiveness and minimal toxicity, itraconazole is the initial drug of choice for dogs and cats with histoplasmosis (see Table 98-2). Animals should be treated for 60 to 90 days or until clinical evidence of disease has been resolved for at least 1 month. Amphotericin B can be used in animals with life-threatening disease or in those unable to absorb oral medications because of intestinal disease. Ketoconazole and fluconazole are also effective in some animals. However, ketoconazole has more adverse effects than itraconazole, and some cases that do not respond to fluconazole respond to intraconazole. The overall success rate for the treatment of histoplasmosis in cats was 33% in one study (Clinkenbeard et al., 1989c). In another study, all eight cats treated with itraconazole (5 mg/kg PO q12h) were eventually cured (Hodges et al., 1994). Pulmonary disease in dogs has a fair to good prognosis, whereas disseminated disease has a poor prognosis.

Administration of glucocorticoids with or without antifungal drugs lessened clinical signs associated with chronic hilar lymphadenopathy much more quickly than did administration of antifungal drugs alone and did not result in disseminated histoplasmosis (Schulman et al., 1999). However, if the infection is active, administration of glucocorticoids may exacerbate clinical disease.

# **Zoonotic Aspects and Prevention**

Like blastomycosis, direct zoonotic transmission from infected animals is unlikely because the yeast phase is not as infectious as the mycelial phase. Care should be taken when culturing the organism. Prevention includes the avoidance of potentially contaminated soil. Organism numbers in contaminated areas can be decreased by application of 3% formalin.

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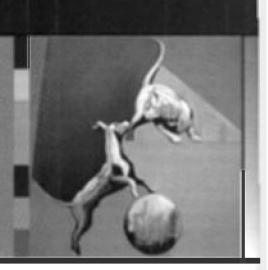
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# CHAPTER QQ

# Polysystemic Protozoal Infections



# CHAPTER OUTLINE

BABESIOSIS
CYTAUXZOONOSIS
HEPATOZOONOSIS
LEISHMANIASIS
NEOSPOROSIS
TOXOPLASMOSIS, FELINE
TOXOPLASMOSIS, CANINE
AMERICAN TRYPANOSOMIASIS

## **BABESIOSIS**

## **Etiology and Epidemiology**

Babesiosis in dogs is most commonly associated with Babesia canis and B. gibsoni, protozoans that parasitize red blood cells (RBCs), leading to progressive anemia. B. canis has worldwide distribution including Africa, Asia, Australia, Europe, Central America, South America, Japan, and the United States. Three subspecies of B. canis have been proposed to be separate species. B. canis rossi is transmitted by Haemaphysalis leachi and is the most pathogenic; B. canis canis is transmitted by Dermacentor reticulatus and is moderately pathogenic; B. canis vogeli is the least pathogenic and is transmitted by *Rhipicephalus sanguineus* (brown dog tick). Babesia canis vogeli is the most common B. canis subspecies infecting dogs in the United States. B. gibsoni infects dogs in the United States, Japan, Sri Lanka, Korea, Malaysia, northern and eastern Africa, Australia, and southern Europe. B. gibsoni strains, of which there are at least three (Asia, California, and Theileria annae, a B. gibsoni-like organism common in dogs in northern Spain), vary genetically (Garcia 2006). Rhipicephalus sanguineus is a proposed vector for B. gibsoni in the United States. Presence of B. gibsoni DNA in dog blood has been associated with a history of a dog bite, especially by an American Pit Bull Terrier, suggesting that fighting is a route of transmission. Babesia spp. infections were detected in 29 states and Ontario (Birkenheuer et al., 2005). Other novel *Babesia* spp. that genetically vary considerably from other *B. canis* or *B. gibsoni* isolates have been described in the United States; however, the prevalence rates for these infections is unknown (Kocan et al., 2001; Meinkoth et al., 2002; Birkenheuer et al. 2004a). None of the *Babesia* spp. that infect cats (*B. cati* [India], *B. felis* [Africa, southern Asia, Europe], *B. herpailuri* [South America, Africa], *B. canis presentii* [Israel]) have been recognized in the United States. *Babesia* spp. can also be transmitted by blood transfusions.

After infection with pathogenic strains of B. canis or B. gibsoni, the incubation period varies from several days to several weeks. The degree of parasitemia varies by the organism studied but can be detected transiently in some dogs as soon as day 1 (Boozer & Macintire, 2003). The organisms replicate intracellularly in RBCs, resulting in intravascular or extravascular hemolytic anemia. Immune-mediated reactions against the parasites or altered self-antigens worsen the hemolytic anemia and commonly result in a positive direct Coombs test. Activation of macrophages leads to fever and hepatosplenomegaly. Severe hypoxia occurs because of rapid breakdown of RBCs. Disseminated intravascular coagulation occurs in some infected dogs during acute infection. The severity of disease depends on the species and strain of Babesia and the host's immune status; chronic, subclinical infection can be common with some. Administration of glucocorticoids or splenectomy may activate chronic disease. Presence of coinfections, such as Bartonella spp., may increase the pathogenic potential (Kordick et al., 1999; Tuttle et al., 2003).

#### **Clinical Features**

In the United States, subclinical *Babesia* spp. infections are most common. Peracute or acute *Babesia* spp. infections result in anemia and fever, leading to pale mucous membranes, tachycardia, tachypnea, depression, anorexia, and weakness. Icterus, petechiae, and hepatosplenomegaly are present in some dogs depending on the stage of infection and the presence of disseminated intravascular coagulation. Severe anemia, disseminated intravascular coagulation, metabolic acidosis, and renal disease are most common during acute infection and are generally most severe with *B. canis* 

rossi infections in South Africa. The main differential diagnosis for acute babesiosis is primary immune-mediated hemolytic anemia. Chronically infected dogs commonly have weight loss and anorexia. Ascites, gastrointestinal signs, CNS disease, edema, and clinical evidence of cardiopulmonary disease occur in some dogs with atypical infection.

# Diagnosis

Regenerative anemia, hyperbilirubinemia, bilirubinuria, hemoglobinuria, thrombocytopenia, metabolic acidosis, azotemia, polyclonal gammopathy, and renal casts are common in dogs infected with pathogenic Babesia spp. Presence of the organism in RBCs detected by Wright's or Giemsa stains on thin blood smears (see Chapter 92) can be used to support the diagnosis, but parasitemia can be intermittent, giving falsely negative results; capillary blood is the preferred source for blood smear evaluation. B. canis is typically found as paired, piriform bodies measuring 2.4 × 5.0 µm. B. gibsoni is typically found as single or paired annular bodies measuring 1.0 × 3.2 µm. Serologic and polymerase chain reaction (PCR) assays are also available to help aid in the diagnosis. Indirect fluorescent antibody tests for B. canis and B. gibsoni are available commercially. However, serologic cross-reactivity can exist between B. canis and B. gibsoni, so antibody test results cannot be used to determine the infective species definitively. Demonstration of increasing titers over 2 to 3 weeks is consistent with recent or active infection. No standardization between laboratories exists, so suggested positive cutoff titers vary. False-negative serologic test results can occur in some dogs, particularly those with peracute disease or concurrent immunosuppression. A titer above 1:320 is suggested as diagnostic for B. gibsoni, but not all infected dogs achieve this titer magnitude (Birkenheuer et al., 1999). Many dogs are seropositive but clinically normal, so serology alone cannot be used to make a definitive diagnosis of clinical babesiosis. Positive results in PCR assays performed on blood prove current infection but positive results do not always correlate with clinical illness.

# Treatment

Supportive care, including blood transfusions, sodium bicarbonate therapy for acidosis, and fluid therapy, should be administered as indicated. A number of drugs, including diminazene aceturate, phenamidine, pentamidine isethionate, parvaquone, atovaquone, and niridazole, have also been used in an attempt to treat different Babesia spp. infections. In the United States, if clinical disease associated with B. canis is suspected, imidocarb diproprionate may be effective when administered (5 to 6.6 mg/kg SC or intramuscularly [IM]) twice, 14 days apart or (7.5 mg/kg, SC or IM) once. Adverse effects include transient salivation, diarrhea, dyspnea, lacrimation, and depression. Imidocarb is not as effective for the treatment of B. gibsoni infection. In the United States, if clinical disease associated with B. gibsoni is suspected, azithromycin (10 mg/kg PO q24h for a minimum of 10 days) or clindamycin hydrochloride (12.5 mg/kg PO q12h for at least 10 days) may lessen clinical disease if other drugs are not available. Azithromycin (as described) and atovaquone (13.3 mg/kg PO q8h for at least 10 days) is currently recommended for the treatment B. gibsoni infections, but this combination does not always result in elimination of infection (Birkenheuer et al., 2004b; Jefferies et al., 2007). Because no drugs are known to eliminate infection consistently, treatment of healthy, seropositive dogs is unlikely to be of benefit.

# **Zoonotic Aspects and Prevention**

No evidence currently exists to suggest that Babesia spp. infecting dogs and cats can cause human disease. However, some Babesia spp. infections of people are genetically similar to those infecting dogs, and the organism should be considered important vector-borne diseases of people. Ticks should be controlled if possible. If controlling ticks is difficult in a B. canis-infected kennel, one dose of imidocarb at 7.5 mg/kg IM may eliminate the carrier state. Minimal cross-protection exists between species; a dog that has recovered from babesiosis may still become ill if infected with another species. Thus tick control must be maintained in endemic areas. Administration of immunosuppressive drugs and splenectomy should be avoided in previously infected dogs. Dogs used as blood donors should be assessed for infection by PCR or serologic screening and positive dogs excluded from the program. Dog bites should be avoided. A B. canis vaccine is available in Europe. For blood donor programs, high-risk breeds (Greyhound, American Pit Bull Terrier) or dogs from endemic areas should be screened for Babesia spp. infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2005).

# **CYTAUXZOONOSIS**

# **Etiology and Epidemiology**

Cytauxzoon felis is a protozoal disease of cats in the southeastern, mid-Atlantic, and south-central United States that is usually fatal. Large-scale prevalence rates have not been performed, but one study of 961 cats in Florida, North Carolina, and Tennessee showed a prevalence rate of 0.3% (Haber et al., 2007). Isolates from domestic cats have been genetically similar between studies (Birkenheuer et al., 2006b). Bobcats are usually subclinically affected and may therefore be the natural host of the organism. The organism can be passed experimentally from infected bobcats to domestic cats by Dermacentor variabilis (American dog tick); clinical illness occurs after an incubation period of 5 to 20 days. After infection, schizonts and macroschizonts form in mononuclear phagocytes. The infected macrophages line the lumen of veins throughout the body. Merozoites released from the infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by the mononuclear infiltrates and from hemolytic anemia. Domestic cats occasionally survive infection, suggesting that variants that are less virulent to cats also exist (Walker et al., 1995; Meinkoth et al., 2000; Haber et al., 2007).

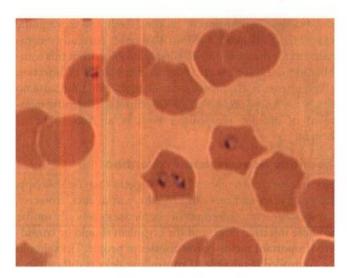


FIG 99-1 Cytauxzoon felis in the red blood cells of a cat. (Courtesy Dr. Terry M. Curtis, Gainesville, FL.)

# **Clinical Features**

Most cases of cytauxzoonosis are in cats allowed to go outdoors. Fever, anorexia, dyspnea, depression, icterus, pale mucous membranes, and death are the most common clinical findings. A primary differential diagnosis is mycoplasmosis. Ticks are rarely identified on affected cats.

# Diagnosis

Regenerative anemia, pancytopenia, and neutrophilic leukocytosis are the most common hematologic findings; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, hyperbilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears (Fig. 99-1) stained with Wright's or Giemsa stains (see Chapter 92). Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates. The organism is easily identified on histopathologic evaluation of most organs. Serologic testing is not commercially available. PCR can be used to amplify organism DNA from blood.

# **Treatment**

Supportive care includes fluid therapy and blood transfusion administered as indicated. Diminazene (five cats) (2.0 mg/kg IM twice, 7 days apart) or imidocarb (one cat) (2 mg/kg IM twice, 14 days apart) was used in cats that survived infection (Greene et al., 1999). Historically, parvaquone (10 to 30 mg/kg IM or SC q24h) administered for 2 to 3 days, buparvaquone (10 mg/kg IM or SC q24h) administered for 2 to 3 days, or thiacetarsemide (0.1 mg/kg IV q12h) administered for 2 days have been attempted. Diminazene, parvaquone, and buparvaquone are not routinely available; thiacetarsemide is toxic for cats and should not be used in this species. If no other drug is available, enrofloxacin at 5.0 mg/kg PO

or SC q12h for 7 to 10 days could be attempted. Azithromycin and atovaquone as used for *B. gibsoni* may be effective.

# **Zoonotic Aspects and Prevention**

Cytauxzoon felis is not known to be zoonotic. The disease can only be prevented by avoiding exposure. Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity.

# **HEPATOZOONOSIS**

# **Etiology and Epidemiology**

Hepatozoonosis in dogs is caused by the protozoal agents Hepatozoon canis and H. americanum. In North America H. americanum predominates, is transmitted by Amblyomma maculatum (Gulf Coast tick), and is most common in the Texas Gulf Coast, Mississippi, Alabama, Georgia, Florida, Louisiana, and Oklahoma. In Africa, southern Europe, and Asia, H. canis predominates and is transmitted by Rhipicephalus sanguineus (brown dog tick). A Hepatozoon species is occasionally found in the blood of cats in Europe. Clinical disease associations are currently unclear, but the cats are commonly coinfected with feline leukemia virus or feline immunodeficiency virus. Vertebrate hosts develop macrogametes and microgametes in neutrophils and monocytes. The tick ingests the organism during a blood meal and oocysts develop. After a dog ingests an infected tick, sporozoites are released and infect mononuclear phagocytes and endothelial cells of the spleen, liver, muscle, lungs, and bone marrow and ultimately form cysts containing macromeronts and micromeronts. Micromeronts develop into micromerozoites, which infect leukocytes and develop into gamonts. Tissue phases induce pyogranulomatous inflammation, resulting in clinical disease. Glomerulonephritis or amyloidosis may occur as a result of chronic inflammation and immune complex disease. Infected dogs can serve as a source of infection for ticks for months to years (Ewing et al., 2003).

# **Clinical Features**

H. americanum can be a primary pathogen, resulting in clinical illness without concurrent immune deficiency. Clinically affected dogs have been in all age groups, but disease is most commonly recognized in puppies. Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, and bloody diarrhea occur in some dogs. Clinical signs can be intermittent and recurrent.

# **Diagnosis**

Neutrophilic leukocytosis (20,000 to 200,000 cells/ L) with a left shift is the most common hematologic finding. Thrombocytopenia is unusual unless coinfection with *Ehrlichia canis* or *Anaplasma* spp. occurs. Normocytic, normochromic, nonregenerative anemia is common and is likely from

chronic inflammation. Increased activity of alkaline phosphatase but not creatine kinase occurs in *H. americanum*—infected dogs. Hypoalbuminemia, hypoglycemia and, rarely, polyclonal gammopathy occur in some dogs. Periosteal reactions from the inflammatory reaction directed at tissue phases in muscle can occur in any bone except the skull, are most common in young dogs, do not occur in every case, and are not pathognomonic for hepatozoonosis. Definitive diagnosis is based on identification of gamonts in neutrophils or monocytes in Giemsa or Leishman's stained blood smears or by demonstration of the organism in muscle biopsy sections. PCR assays may be used to aid in the diagnosis in the future.

#### **Treatment**

No therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues. However, clinical disease resolves rapidly with several drug protocols. For treatment of *H. americanum*, the combination of trimethoprim-sulfadiazine (15 mg/kg PO q12h), pyrimethamine (0.25 mg/kg PO q24h), and clindamycin (10 mg/kg PO q8h) for 14 days is highly successful in the acute stage (Macintire et al., 2001). Use of decoquinate (10 to 20 mg/kg q12h) with food lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate (5 to 6 mg/kg IM or SC) administered once or twice 14 days apart is the drug of choice for treatment of *H. canis* and may also be effective for *H. americanum*. Administration of nonsteroidal antiinflammatory agents may lessen discomfort for some dogs.

# **Zoonotic Aspects and Prevention**

No evidence exists for zoonotic transfer of *H. americanum* or *H. canis* from infected dogs to people. Tick control is the best form of prevention. Glucocorticoid administration should be avoided because it may exacerbate clinical disease.

# **LEISHMANIASIS**

# Etiology and Epidemiology

Leishmania spp. are flagellates that cause cutaneous, mucocutaneous, and visceral diseases in dogs, human beings, and other mammals. Rodents and dogs are primary reservoirs of Leishmania spp., people and cats are probably incidental hosts, and sandflies are the vector in most endemic regions other than the United States. Leishmaniasis was considered unimportant in the United States until recently, with cases only reported occasionally. In 1999 L. donovani infection was confirmed in multiple dogs in a Foxhound kennel in New York state (Gaskin et al., 2002). Further investigation of more than 12,000 foxhounds and other canids documented L. donovani infection in 18 states and two Canadian provinces (Duprey et al., 2006) (Fig. 99-2). Infection of canids other than Foxhounds appears to be uncommon. In other countries flagellated promastigotes develop in the sandfly and are



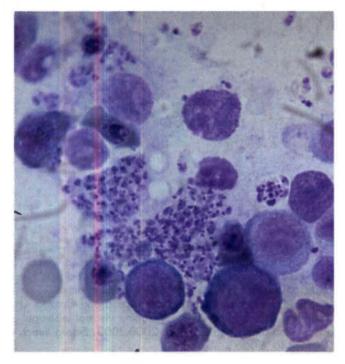
#### FIG 99-2

Distribution of hunt clubs with confirmed cases of visceral leishmaniasis, United States and Canada. States in which hunt clubs or kennels had 1 or more dogs infected with Leishmania infantum are shaded. Leishmania-positive Foxhounds were also found in Nova Scotia and Ontario. (Reprinted from Duprey ZH et al: Canine visceral leishmaniasis, United States and Canada, 2000-2003, Emerg Infect Dis 12:440, 2006.)

injected into the vertebrate host when the sandfly feeds. Promastigotes are engulfed by macrophages and disseminate through the body. After an incubation period of 1 month to 7 years, amastigotes (nonflagellate) form and cutaneous lesions develop; sandflies are infected during feeding. In Foxhounds in the United States transmission appeared to be primarily from dog to dog (Duprey et al., 2006). Transmission by fighting, shared needles, blood transfusions, breeding, and congenital transmission can occur (Duprey et al., 2006; de Freitas et al., 2006). The intracellular organism induces extreme immune responses; polyclonal gammopathies (and occasionally monoclonal); proliferation of macrophages, histiocytes, and lymphocytes in lymphoreticular organs; and immune complex formation resulting in glomerulonephritis and polyarthritis are common.

#### Clinical Features

Dogs generally develop visceral leishmaniasis. A subclinical phase of infection may persist for months or years. Weight loss in the face of a normal to increased appetite, polyuria, polydipsia, muscle wasting, depression, vomiting, diarrhea, cough, petechiae, ecchymosis, epistaxis, sneezing, and melena are common presenting complaints. Splenomegaly, lymphadenopathy, facial alopecia, fever, rhinitis, dermatitis, increased lung sounds, icterus, swollen painful joints, uveitis, and conjunctivitis are commonly identified on physical examination. Cutaneous lesions are characterized by hyperkeratosis, scaling, thickening, mucocutaneous ulcers, and intradermal nodules on the muzzle, pinnae, ears, and foot pads. Bone lesions are detected in some dogs. Most dogs die or are euthanized as a consequence of chronic kidney disease. Cats are usually subclinically infected; one cat in Texas had cutaneous nodules on the pinna.



Impression smear of a lymph node of a Leishmania spp – infected dog showing intracellular amastigates. (Courtesy Dr. Arturo Font, Barcelona, Spain.)

# **Diagnosis**

The principal clinicopathologic abnormalities include hyperglobulinemia, hypoalbuminemia, proteinuria, increased liver enzyme activities, thrombocytopenia, azotemia, lymphopenia, and leukocytosis with left shift. The hyperglobulinemia is usually polyclonal, but an IgG monoclonal gammopathy was reported in a dog (Font et al., 1994). Neutrophilic polyarthritis occurs in some dogs as a manifestation of a type III hypersensitivity reaction. Demonstration of amastigotes (2.5 to 5.0 µm ×1.5 to 2.0 µm) in lymph node aspirates, bone marrow aspirates, or skin imprints stained with Wright's or Giemsa stain gives a definitive diagnosis (Fig. 99-3). The organism can also be identified by histopathologic or immunoperoxidase evaluation of skin or organ biopsy, culture, inoculation of hamsters, or PCR. Antibodies against Leishmania can be detected in serum; IgG titers develop 14 to 28 days after infection and decline 45 to 80 days after treatment. Serologic cross-reactivity occurs between Trypanosoma cruzi and Leishmania. Because dogs are unlikely to eliminate infection spontaneously, most true-positive antibody test dogs are currently infected. PCR can be performed on ethylenediamine tetraacetic acid anticoagulated blood, bone marrow, or lymph node aspirates. Real-time PCR assays can be used to monitor response to therapy (Francino et al., 2006).

#### **Treatment**

Although clinical signs of disease often improve with drug administration, the prognosis for visceral leishmaniasis in dogs is variable; most cases are recurrent. No drug or drug combination has been used to clear Leishmania from the body successfully. The combination of antimony and allopurinol (15 mg/kg PO q12h) was superior to treatment with either drug alone (Denerolle et al., 1999), but even long-term therapy does not always eliminate infection (Manna et al., 2007). Because antimony drugs are not available in the United States, infected dogs should be started on allopurinol therapy initially. In one study, marbofloxacin was effective in vitro and may be considered for the treatment of infected dogs if other drugs are not available (Vouldoukis et al., 2006). Liposomal or lipid-emulsified amphotericin B at varying doses (0.8 to 3.3 mg/kg IV for varying numbers of treatments) has been prescribed with good clinical results, but recurrences can still occur (Oliva et al., 1995; Corcadillas et al., 2003). Dogs with chronic kidney disease have a poor prognosis, but a recent study showed administration of allopurinol to be beneficial (Plevraki et al., 2006).

# **Zoonotic Aspects and Prevention**

The primary zoonotic risk for canine leishmaniasis is from dogs acting as a reservoir host for the organism. Direct contact with amastigotes in draining lesions is unlikely to result in human infection. None of the 185 persons with potential exposure to infected Foxhounds had evidence of infection (Duprey et al., 2006). Avoidance of infected sandflies is the only means of prevention. If in endemic areas, house animals during night hours and control breeding places of sandflies. Use of 10% imidacloprid/50% permethrin may lessen transmission in sandfly-endemic areas (Otranto et al., 2007). A vaccine is available for use with dogs in some countries (Dantas-Torres, 2006). For blood donor programs, high-risk breeds (e.g., Foxhounds) or dogs from endemic areas should be screened for Leishmania spp. infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2005).

#### NEOSPOROSIS

# **Etiology and Epidemiology**

*Neospora caninum* is a coccidian previously confused with *T*. gondii because of similar morphology. The sexual cycle is completed in the gastrointestinal tract of dogs and results in the passage of oocysts in feces. Oocyst shedding can continue for several months in some dogs (McGarry et al., 2003). Sporozoites develop in oocysts within 24 hours of passage. Tachyzoites (rapidly dividing stage) and tissue cysts containing hundreds of bradyzoites (slowly dividing stage) are the other two life stages. Dogs are infected by ingestion of bradyzoites but not tachyzoites. Infection has been documented after ingestion of infected bovine placental tissue. Dogs can become infected from ingesting intermediate hosts such as white-tailed deer (Gondim et al., 2004). Thus free-roaming dogs may be at increased risk of infection. Transplacental infection has been well documented; dams that give birth to infected offspring can repeat transplacental infection during

subsequent pregnancies. Because repeated transplacental infections occur, puppies from a bitch who previously birthed infected puppies are at an increased risk. Canine neosporosis has been reported in many countries around the world. Seroprevalence of infection has varied from 0% to 100% depending on the country and lifestyle of the dog (Dubey et al., 2007a). The pathogenesis of the disease is primarily related to the intracellular replication of tachyzoites. Although organism replication occurs in many tissues, including the lungs, in dogs clinical illness is primarily neuromuscular.

Encephalomyelitis and myositis develop in experimentally infected kittens and seropositive, naturally exposed cats have been detected (Bresciani et al., 2007), but clinical disease in naturally infected cats has not been reported. *N. caninum* seropositive, nondomestic felids also have been reported (Spencer et al., 2003).

Administration of glucocorticoids may activate bradyzoites in tissue cysts, resulting in clinical illness.

#### **Clinical Features**

Ascending paralysis with hyperextension of the hindlimbs in congenitally infected puppies is the most common clinical manifestation of the disease. Muscle atrophy occurs in many cases. Polymyositis and multifocal CNS disease can occur alone or in combination. Clinical signs can be evident soon after birth or may be delayed for several weeks. Neonatal death is common. Although disease tends to be most severe in congenitally infected puppies, dogs as old as 15 years have been clinically affected. In one dog presented primarily for respiratory disease, cough was the principal sign. Myocarditis, dysphagia, ulcerative dermatitis, pneumonia, and hepatitis occur in some dogs. Whether clinical disease in older dogs is from acute, primary infection or exacerbation of chronic infection is unknown. Administration of glucocorticoids may activate bradyzoites in tissue cysts, resulting in clinical illness. Disease is caused by intracellular replication of Neospora caninum tachyzoites. Infection of CNS structures causes mononuclear cell infiltrates, which suggests an immune-mediated component to the pathogenesis of disease. Intact tissue cysts in neural structures are generally not associated with inflammation, but ruptured tissue cysts induce inflammation. Untreated disease generally results in death.

# **Diagnosis**

Hematologic and biochemical findings are nonspecific. Myositis commonly results in increased creatine kinase and aspartate aminotransferase activities. CSF abnormalities include increased protein concentration (20 to 50 mg/dL) and a mild, mixed inflammatory cell pleocytosis (10 to 50 cells/ L) consisting of monocytes, lymphocytes, neutrophils and, rarely, eosinophils. Interstitial and alveolar patterns can be noted on thoracic radiographs.

Definitive diagnosis is based on demonstration of the organism in CSF or tissues. Tachyzoites are rarely identified on cytologic examination of CSF, imprints of dermatologic lesions, and bronchoalveolar lavage. Mixed inflammation with neutrophils, lymphocytes, eosinophils, plasma cells,

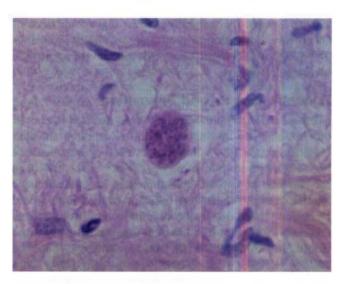


FIG 99-4
Neospora caninum cyst filled with bradyzoites in canine central nervous system tissue.

macrophages, and tachyzoites was noted on transthoracic aspirate of one dog with lung disease. *Neospora caninum* tissue cysts have a wall thicker than 1  $\mu$ m; *T. gondii* tissue cysts have a wall thinner than 1  $\mu$ m (Fig. 99-4). Oocysts can be detected in feces by microscopic examination after flotation or by PCR. The organism can be differentiated from *T. gondii* by electron microscopy, immunohistochemistry, and PCR. A multiplex PCR assay that detects both *T. gondii* and *N. caninum* for use with tissues or CSF has been reported (Schatzerg et al., 2003)

A presumptive diagnosis of neosporosis can be made by combining appropriate clinical signs of disease and positive serology or presence of antibodies in CSF with the exclusion of other etiologies inducing similar clinical syndromes, particularly *T. gondii*. Serologic cross-reactivity between *T. gondii* and *N. caninum* exist in some assays (Silva et al., 2007). IgG antibody titers of at least 1:200 have been detected in most dogs with clinical neosporosis; minimal serologic cross-reactivity occurs with *T. gondii* at titers of 1:50 or higher when using the immunofluorescent assay test.

#### **Treatment**

Although many dogs with neosporosis die, some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine; sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine; or clindamycin alone. Administration of trimethoprim-sulfadiazine (15 mg/kg PO q12h) with pyrimethamine (1 mg/kg PO q24h) for 4 weeks or clindamycin (10 mg/kg PO q8h) for 4 weeks was recommended for the treatment of canine neosporosis. In one recent study of naturally infected beagle puppies, administration of clindamycin alone (75 mg/puppy at 9 weeks of age, PO, q12h [dose doubled at 13 weeks] for 6 months) lessened clinical signs of disease but did not eliminate the infection (Dubey et al.,

2007b). Treatment of clinically affected dogs should be initiated before the development of extensor rigidity, if possible. The prognosis for dogs presented with severe neurologic involvement is grave.

# **Zoonotic Aspects and Prevention**

Neospora caninum antibodies have been detected in people, but in one study no link was found to repeated abortion (Peterson et al., 1999). In addition, the organism has not been isolated from human tissues (Dubey et al., 2007a), so the zoonotic potential is still unproven. An epidemiologic link has been shown between dogs and cattle; efforts should be made to lessen dog fecal contamination of livestock feed, and dogs should not be allowed to ingest bovine placentas. Consuming raw meat is a risk factor for dogs and should be avoided (Reichel et al., 2007). Hunting behavior of dogs should be restricted if possible. Bitches that whelp clinically affected puppies should not be bred. Glucocorticoids should not be administered to seropositive animals, if possible, because a potential exists for activation of infection.

# FELINE TOXOPLASMOSIS

# **Etiology and Epidemiology**

Toxoplasma gondii is one of the most prevalent parasites infecting warm-blooded vertebrates. Only cats complete the coccidian life cycle and pass environmentally resistant oocysts in feces. Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity. Tachyzoites disseminate in blood or lymph during active infection and replicate rapidly intracellularly until the cell is destroyed. Bradyzoites are the slowly dividing, persistent tissue stage that form in the extraintestinal tissues of infected hosts as immune responses attenuate tachyzoite replication. Tissue cysts form readily in the CNS, muscles, and visceral organs. Bradyzoites may persist in tissues for the life of the host.

Infection of warm-blooded vertebrates occurs after ingestion of any of the three life stages of the organism or transplacentally. Most cats are not coprophagic and so are infected most commonly by ingesting T. gondii bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants (Fig. 99-5). Results of a recent study confirm that the T. gondii oocyst shedding prepatent period is stage dependent (ingestion of bradyzoites has a shorted prepatent period than ingestion of sporozoites) and not dose dependent (Dubey, 2006). In addition, transmission of T. gondii is most efficient when cats consume tissue cysts (carnivorism) and when intermediate hosts consume oocysts (fecal-oral transmission). T. gondii infection of rodents changes the behavior of the prey species, making it less averse to cats, potentially increasing the likelihood the definitive host (felid) will become infected and potentiate the sexual phase of the organism (Vyas et al., 2007). Approximately 30% to 40% of

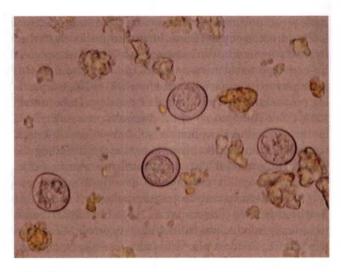


FIG 99-5 Unstained *Toxoplasma gondii* unsporulated oocysts. The oocysts are  $10 \times 12 \ \mu m$ .

cats and people in the United States are seropositive and are presumed to be infected. In a recent study of clinically ill cats, *T. gondii* antibodies were detected in 31.6% of the 12,628 cats tested (Vollaire et al., 2005).

#### **Clinical Features**

Approximately 10% to 20% of experimentally inoculated cats develop self-limiting, small-bowel diarrhea for 1 to 2 weeks after primary oral inoculation with *T. gondii* tissue cysts; this is presumed to be from enteroepithelial replication of the organism. However, detection of *T. gondii* oocysts in feces is rarely reported in studies of naturally exposed cats with diarrhea. *T. gondii* enteroepithelial stages were found in intestinal tissues from two cats with inflammatory bowel disease. Positive response to anti-*Toxoplasma* drugs in these two cats suggests that toxoplasmosis may occasionally induce inflammatory bowel disease. Eosinophilic fibrosing gastritis was recently described in a *T. gondii*—infected cat (McConnell et al., 2007).

Fatal extraintestinal toxoplasmosis can develop from overwhelming intracellular replication of tachyzoites after primary infection; hepatic, pulmonary, CNS, and pancreatic tissues are commonly involved. Kittens infected by the transplacental or transmammary routes develop the most severe signs of extraintestinal toxoplasmosis and generally die of pulmonary or hepatic disease. Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, and fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea. If a host with chronic toxoplasmosis is immunosuppressed, bradyzoites in tissue cysts can replicate rapidly and disseminate again as tachyzoites; this is common in people with acquired immunodeficiency syndrome (AIDS). Disseminated toxoplasmosis has been documented in cats concurrently infected with feline leukemia, feline immunodeficiency, or feline infectious peritonitis viruses as well as after cyclosporine administration for skin

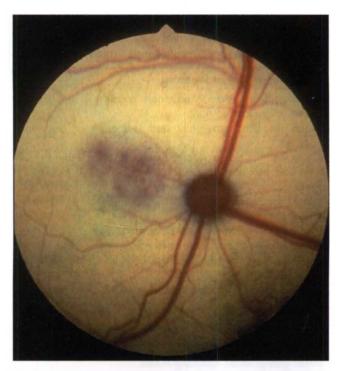


FIG 99-6
Punctate chorioretinitis caused by *Toxoplasma gondii* in an experimentally inoculated cat.

disease or after renal transplantation (Bernstein et al., 1999; Barrs et al., 2006).

Sublethal, chronic toxoplasmosis occurs in some cats. *T. gondii* infection should be on the differential diagnosis list for cats with anterior or posterior uveitis, cutaneous lesions, fever, muscle hyperesthesia, myocarditis with arrhythmias, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, or pancreatitis (Fig. 99-6). Based on results of *T. gondii*–specific aqueous humor antibody and PCR studies, toxoplasmosis appears to be a common infectious cause of uveitis in cats. Kittens infected transplacentally or lactationally commonly develop ocular disease. Immune complex formation and deposition in tissues and delayed hypersensitivity reactions may be involved in chronic, sublethal clinical toxoplasmosis. Because none of the anti-*Toxoplasma* drugs totally clear the body of the organism, recurrence of disease is common.

# **Diagnosis**

Cats with clinical toxoplasmosis can have a variety of clinicopathologic and radiographic abnormalities, but none documents the disease. Nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, and bilirubinuria as well as increases in serum protein and bilirubin concentrations, creatinine kinase, alanine aminotransferase, alkaline phosphatase, and lipase activities occur in some cats. Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns or pleural effusion. Mass lesions may be detected on computed tomography or magnetic resonance

imaging examinations. CSF protein concentrations and cell counts are often higher than normal. The predominant white blood cells in CSF are small mononuclear cells, but neutrophils also are commonly found.

The antemortem definitive diagnosis of feline toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon, particularly in association with sublethal disease. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF. Detection of  $10 \times 12~\mu m$  oocysts in feces in cats with diarrhea suggests toxoplasmosis but is not definitive because *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts.

T. gondii-specific antibodies (IgM, IgG, IgA), antigens, and immune complexes can be detected in the serum of normal cats as well as in those with clinical signs of disease, so antemortem diagnosis of clinical toxoplasmosis is impossible based on these tests alone. Of the serum tests, IgM correlates the best with clinical feline toxoplasmosis because this antibody class is rarely detected in serum of healthy cats. The antemortem diagnosis of clinical toxoplasmosis can be tentatively based on the combination of the following:

- Demonstration of antibodies in serum, which documents exposure to *T. gondii*
- Demonstration of an IgM titer above 1:64 or a fourfold or greater increase in IgG titer, which suggests recent or active infection
- · Clinical signs of disease referable to toxoplasmosis
- Exclusion of other common causes for the clinical syndrome
- · Positive response to appropriate treatment

Some cats with clinical toxoplasmosis will have reached their maximal IgG titer or have undergone antibody class shift from IgM to IgG by the time they are serologically evaluated, so the failure to document an increasing IgG titer or a positive IgM titer does not exclude the diagnosis of clinical toxoplasmosis. Because some healthy cats have extremely high serum antibody titers and some clinically ill cats have low serum antibody titers, the magnitude of titer is relatively unimportant in the clinical diagnosis of toxoplasmosis. Because the organism cannot be cleared from the body, most cats will be antibody positive for life, so repeating serum antibody titers after the clinical disease has resolved is not necessary.

The combination of aqueous humor or CSF *T. gondii*-specific antibody detection and organism DNA detection by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis (e.g., Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins). Whereas *T. gondii*-specific IgA, IgG, and organism DNA can be detected in aqueous humor and CSF of both normal and clinically ill cats, *T. gondii*-specific IgM has only been detected in the aqueous humor or CSF of clinically ill cats and therefore may be the best indicator of clinical disease. Because *T. gondii* DNA can be detected

in the blood of healthy cats, positive PCR results do not correlate to clinical disease (Burney et al., 1999).

#### **Treatment**

Supportive care should be instituted as needed. Clindamycin hydrochloride (10 to 12 mg/kg PO q12h) administered for 4 weeks or a trimethoprim-sulfonamide combination (15 mg/ kg PO q12h) administered for 4 weeks has been used most frequently by the author for the treatment of clinical feline toxoplasmosis. Azithromycin (10.0 mg/kg PO q24h) has been used successfully in a limited number of cats, but the optimal duration of therapy is unknown. Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in toxicity in cats. Cats with systemic clinical signs of toxoplasmosis, such as fever or muscle pain combined with uveitis, should be treated with anti-Toxoplasma drugs in combination with topical, oral, or parenteral corticosteroids to avoid secondary lens luxations and glaucoma. T. gondii-seropositive cats with uveitis that are otherwise normal can be treated with topical glucocorticoids alone unless the uveitis is recurrent or persistent. In these situations, administration of a drug with anti-T. gondii activity may be beneficial.

Clinical signs not involving the eyes or the CNS usually resolve within the first 2 to 3 days of clindamycin or trimethoprim-sulfonamide administration; ocular and CNS toxoplasmosis responds more slowly to therapy. If fever or muscle hyperesthesia does not decrease after 3 days of treatment, other causes should be considered. Recurrence of clinical signs may be more common in cats treated for less than 4 weeks. No evidence suggests that any drug can totally clear the body of the organism, so recurrences are common and infected cats will always be seropositive. The prognosis is poor for cats with hepatic or pulmonary disease caused by organism replication, particularly in those that are immunocompromised.

#### **Zoonotic Aspects and Prevention**

T. gondii is a major zoonosis. Primary infection of mothers during gestation can lead to clinical toxoplasmosis in the fetus; stillbirth, CNS disease, and ocular disease are common clinical manifestations. Primary infection in immunocompetent individuals results in self-limiting fever, malaise, and lymphadenopathy. As T-helper cell counts decline, approximately 10% of people with AIDS develop toxoplasmic encephalitis from activation of bradyzoites in tissue cysts.

People most commonly acquire toxoplasmosis transplacentally or by ingesting sporulated oocysts or tissue cysts. To prevent toxoplasmosis, avoid eating undercooked meats or ingesting sporulated oocysts (Box 99-1). In a recent study of 6282 meat samples from 698 retail meat stores, *T. gondii* was detected by bioassay in cats in none of the beef or chicken samples tested and only a small number of pork samples (Dubey et al., 2005). Although owning a pet cat was epidemiologically associated with acquiring toxoplasmosis in one study of pregnant women, touching individual cats is prob-



## Prevention of Human Toxoplasmosis

#### **Prevention of Oocyst Ingestion**

Avoid feeding undercooked meats to cats.

Do not allow cats to hunt.

Clean the litter box daily and incinerate or flush the faces.

Clean the litter box periodically with scalding water or use a litter box liner.

Wear gloves when working with soil.

Wash hands thoroughly with soap and hot water after gardening.

Wash fresh vegetables well before ingestion.

Keep children's sandboxes covered.

Boil water for drinking that has been obtained from the general environment.

Control potential transport hosts.

Treat oocyst shedding cats with anti-Toxoplasma drugs.

#### **Prevention of Tissue Cyst Ingestion**

Cook all meat products to 66° C.

Wear gloves when handling meats.

Wash hands thoroughly with soap and hot water after handling meats.

Freeze all meat for a minimum of 3 days before cooking.

ably not a common way to acquire toxoplasmosis for the following reasons:

- Cats generally only shed oocysts for days to several weeks after primary inoculation.
- Repeat oocyst shedding is rare, even in cats receiving glucocorticoids, cyclosporine, or in those infected with feline immunodeficiency virus or feline leukemia virus.
- Cats with toxoplasmosis inoculated with tissue cysts 16 months after primary inoculation did not shed oocysts.
- Cats are quite fastidious and usually do not allow feces to remain on their skin for periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.
- Increased risk of acquired toxoplasmosis was not associated with cat ownership in people with AIDS or in veterinary health care providers.

However, because some cats will repeat oocyst shedding when exposed a second time, feces should always be handled carefully. If a fecal sample from a cat is shown to contain oocysts measuring  $10 \times 12~\mu m$ , the organism is assumed to be *T. gondii*. The feces should be collected daily until the oocyst shedding period is complete; administration of clindamycin (25 to 50 mg/kg PO divided q12h) or sulfonamides (100 mg/kg PO divided q12h) can reduce levels of oocyst shedding.

Because human beings are not commonly infected with *T. gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. Fecal examination is an adequate procedure to determine when cats are actively shedding oocysts but cannot predict when a cat has shed oocysts in the past. No serologic assay accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding; most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their physician for testing.

# CANINE TOXOPLASMOSIS

# **Etiology and Epidemiology**

Dogs do not produce *T. gondii* oocysts like cats, but they can mechanically transmit oocysts after ingesting feline feces. The tissue phases of *T. gondii* infection occur in dogs and can induce clinical disease. Approximately 20% of dogs in the United States are seropositive for *T. gondii* antibodies. Before 1988 many dogs diagnosed with toxoplasmosis based on histologic evaluation were truly infected with *Neospora caninum* (see Neosporosis section).

#### **Clinical Features**

Respiratory, gastrointestinal, or neuromuscular infection resulting in fever, vomiting, diarrhea, dyspnea, and icterus occurs most commonly in dogs with generalized toxoplasmosis. Generalized toxoplasmosis is most common in immunosuppressed dogs, such as those with canine distemper virus infection or those receiving cyclosporine to prevent rejection of a transplanted kidney. Neurologic signs depend on the location of the primary lesions and include ataxia, seizures, tremors, cranial nerve deficits, paresis, and paralysis. Dogs with myositis present with weakness, stiff gait, or muscle wasting. Rapid progression to tetraparesis and paralysis with lower motor neuron dysfunction can occur. Some dogs with suspected neuromuscular toxoplasmosis probably had neosporosis. Myocardial infection resulting in ventricular arrhythmias occurs in some infected dogs. Dyspnea, vomiting, or diarrhea occurs in dogs with polysystemic disease. Retinitis, anterior uveitis, iridocyclitis, and optic neuritis occur in some dogs with toxoplasmosis, but they are less common than in cats. Cutaneous disease has also been detected (Webb et al., 2005).

# Diagnosis

As in cats, hematologic, biochemical, urinalysis, and radiographic abnormalities are not specific. Increased protein concentrations and mixed inflammatory cell infiltrates occur in dogs with CNS toxoplasmosis.

Demonstration of the organism associated with inflammation in tissues or exudates can lead to a definitive diagnosis. More commonly an antemortem diagnosis is based on the combination of appropriate clinical signs, exclusion of other likely etiologies, positive serum antibody tests, exclusion of *N. caninum* infection by serologic testing, and response to an anti-*Toxoplasma* drug. Interpretation of serum, aqueous humor, and CSF antibody and PCR test results is as discussed for toxoplasmosis in cats.

# **Therapy**

Clindamycin hydrochloride (10-12 mg/kg PO q12h) has been used most frequently for treatment of canine toxoplasmosis by the author. Trimethoprim-sulfa (15 mg/kg PO q12h) is an alternative protocol. Treatment should be continued for a minimum of 4 weeks. If uveitis occurs, topical glucocorticoid treatment should also be used.

# **Zoonotic Aspects and Prevention**

Dogs do not complete the enteroepithelial phase of *T. gondii* but can mechanically transmit oocysts after ingesting feline feces. Like all other warm-blooded vertebrates, dogs are infected by the ingestion of sporulated oocysts or tissue cysts. Toxoplasmosis in dogs can be prevented by not allowing dogs to be coprophagic and to feed only cooked meat and meat byproducts.

#### AMERICAN TRYPANOSOMIASIS

# Etiology and Epidemiology

Trypanosoma cruzi is a flagellate that infects many mammals and causes American trypanosomiasis. The disease is diagnosed primarily in South America, but several cases have been detected in dogs of North America. Infected reservoir mammals (dogs, cats, raccoons, opossums, armadillos) and vectors (reduviid [kissing] bugs) are found in the United States, but infection in dogs or people is rare; this may relate to differences in vector behavior and sanitation standards in the United States. In one study in Texas the number of serologically positive dogs increased between 1987 and 1996 (Meurs et al., 1998). Foxhounds infected with Leishmania spp. were recently shown to be coinfected with T. cruzi (Duprey et al., 2006) (Fig. 99-7). The organism has three life stages: trypomastigotes (flagellated stage found free in blood), amastigotes (nonflagellated intracellular form), and epimastigotes (flagellated form found in the vector). When infected kissing bugs defecate during feeding, epimastigotes enter the vertebrate host, infect macrophages and myocytes, and transform into amastigotes. Amastigotes divide by binary fission until the host cell ruptures, releasing trypomastigotes into the circulation. The vector is then infected by ingesting trypomastigotes during a blood meal. Transmission can also occur transplacentally by vector ingestion, blood transfusion, or ingestion of infected tissues or milk. Peak parasitemia occurs 2 to 3 weeks after infection, causing acute disease. Disease in dogs is primarily a cardiomyopathy that develops from parasiteinduced damage to myocardial cells or immune-mediated reactions.



Distribution of hunt clubs with *Trypanosoma cruzi*–positive hounds, United States and Canada. States in which hunt clubs or kennels had 1 or more dogs infected with *T. cruzi* are shaded. A *T. cruzi*–positive hunt club was also found in Ontario. {Reprinted from Duprey ZH et al: Canine visceral leishmaniasis, United States and Canada, 2000-2003,

#### **Clinical Features**

Emerg Infect Dis 12:440, 2006.)

Exercise intolerance and weakness are nonspecific presenting complaints that relate to myocarditis or heart failure during acute infection. Generalized lymphadenopathy, pale mucous membranes, tachycardia, pulse deficits, hepatomegaly, and abdominal distension can be detected on physical examination. Anorexia, diarrhea, and neurologic signs occasionally occur. Dogs that survive acute infection can present for evaluation of chronic dilative cardiomyopathy. In one study of 11 dogs with chronic infection, right-sided cardiac disease, conduction disturbances, ventricular arrhythmias, and supraventricular arrhythmias were most common (Meurs et al., 1998).

#### Diagnosis

Common clinicopathologic abnormalities include lymphocytosis and increased activities of liver enzymes and creatine kinase. Thoracic radiographic, abdominal radiographic, and echocardiographic findings are consistent with cardiac disease and failure but are not specific for trypanosomiasis. The primary electrocardiographic findings are ventricular premature contractions, heart block, and T-wave inversion. Definitive diagnosis is based on organism demonstration. Trypomastigotes (one flagellum, 15 to 20 µm long) can be identified during acute disease on thick blood film (see Chapter 92) or buffy coat smears stained with Giemsa or Wright's stain. The organism is sometimes detected in lymph node aspirates or abdominal effusions. Histopathologic evaluation of cardiac tissue may reveal amastigotes (1.5 to 4.0 μm). Trypomastigotes can also be cultured from blood or grown by bioassay in mice. PCR assays can also be used to prove infection (Nabity et al., 2006).

#### **Treatment**

Nifurtimox has been prescribed most frequently for Chagas disease but are toxic and not routinely available in the United States. In a recent study of allopurinol for the treatment of *T. cruzi* infection in an experimentally infected mouse model, a positive response was noted. Thus treating clinically affected dogs with allopurinol as described for *Leishmania* may be prudent. Glucocorticoid therapy may improve survival of infected dogs. Therapy for arrhythmias or heart failure should be instituted as needed. Most dogs that survive acute infection develop dilative cardiomyopathy. Survival time in 11 dogs ranged from 0 to 60 months (Meurs et al., 1998).

# **Zoonotic Aspects and Prevention**

Infected dogs can serve as a reservoir of *T. cruzi* for vectors, and blood from infected dogs can be infectious to human beings. Vector control is the primary means of prevention. In one recent study use of deltamethrin-treated collars reduced *Triatoma infestans* feeding success on dogs (Reithinger et al., 2005). Dogs should be kept from other reservoir hosts, such as opossums, and should not be fed raw meat. Potential blood donors from endemic areas should be serologically screened. For blood donor programs, high-risk breeds (e.g., Foxhounds) or dogs from endemic areas should be screened for *T. cruzi* infection by serology or PCR assays, and positive dogs should be excluded from the program (Wardrop et al., 2005).

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# CHAPTER 100 Zoonoses

# CHAPTER OUTLINE

**ENTERIC ZOONOSES** 

Nematodes

Cestodes

Coccidians

Flagellates, Amoeba, and Ciliates

Bacteria

BITE, SCRATCH, OR EXUDATE EXPOSURE ZOONOSES

Bacteria

Fungi

Viruses

RESPIRATORY TRACT AND OCULAR ZOONOSES

Bacteria

Viruses

GENITAL AND URINARY TRACT ZOONOSES SHARED VECTOR ZOONOSES SHARED ENVIRONMENT ZOONOSES

Zoonotic diseases are defined as being common to, shared by, or naturally transmitted between humans and other vertebrates. Most of the agents discussed in this chapter can infect and cause disease in immunocompetent people, but disease is generally more prevalent or more severe in immunodeficient people. Immunosuppression is common in humans. People with acquired immunodeficiency syndrome (AIDS) are discussed most frequently, but the population also includes the very old, the very young, and those receiving chemotherapy for immune-mediated diseases, organ transplantation, or neoplasia. Immunosuppressed people are sometimes advised to give up their pets. However, humans are unlikely to contract zoonotic diseases from contact with their pets, so in most cases this is not necessary. The Centers for Disease Control and Prevention online publication Preventing Infections from Pets: A Guide for People with HIV Infection states, "You do not have to give up your pet" (http:// www.cdc.gov/hiv/pubs/brochure/oi\_pets.htm). I believe that all human and other animal health care providers should provide accurate information to pet owners concerning the risks and benefits of pet ownership so that an informed decision about acquiring and keeping pets can be made (Grant et al., 1999).

Many infectious agents can infect humans by direct contact with pets, their exudates, or their excrement. These agents are the most important to veterinary health care providers and to dog and cat owners and are discussed in this chapter by likely route of exposure. For some zoonoses, including Rickettsia rickettsii, Ehrlichia spp., Bartonella spp., and Borrelia burgdorferi, the pet brings the vector of the organism into the environment, resulting in exposure of the person. With other zoonoses, including Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, and Cryptococcus neoformans, the owner and pet are infected by shared environmental exposure to the agent.

Following is a brief description of the more common canine and feline zoonoses encountered in small animal practice. General guidelines for the avoidance of zoonotic transfer of disease for veterinarians and pet owners are listed in Boxes 100-1 and 100-2, respectively.

# **ENTERIC ZOONOSES**

Multiple infectious agents of the gastrointestinal tract can be shared between animals and humans. Prevalences recently reported in two studies in cats and one in dogs are listed in Table 100-1. These findings emphasize that diagnostic workups for enteric infections are indicated because of potential human health risks. The minimal diagnostic plan to assess for enteric zoonoses includes a fecal flotation, fecal wet mount, rectal cytology, and *Cryptosporidium* spp. screening procedure. Fecal culture should be considered if infection with *Salmonella* spp. or *Campylobacter* spp. is on the list of differential diagnoses.

# **NEMATODES**

Visceral larva migrans can be induced by infection of humans with *Toxocara cati, Toxocara canis*, or *Baylisascaris procyonsis* (Table 100-2). In the United States infection of humans is



# BOX 100-1

# General Guidelines for Veterinarians to Avoid Zoonotic Transfer of Disease

- Veterinarians and their staff should familiarize themselves with zoonotic issues and take an active role in discussing the health risks and benefits of pet ownership with clients so that logical decisions concerning ownership and management of individual animals can be made.
- The veterinary clinic should communicate that the staff understands conditions associated with immune deficiency, is discreet, and is willing to help; signs or posters can be effective for this purpose.
- Pet owners should be provided information concerning veterinary or public health aspects of zoonoses, but veterinarians should not diagnose diseases in humans or discuss specific treatments.
- Clinically ill pet owners should always be referred to a physician for additional information and treatment.
- Veterinarians and physicians have different experiences concerning zoonoses; veterinarians should volunteer to speak to the pet owner's physician to clarify zoonotic issues when indicated.
- When public health-related advice is offered, it should be documented in the medical record.
- When reportable zoonotic diseases are diagnosed, appropriate public health officials should be contacted.
- Diagnostic plans to assess for presence of organisms with zoonotic potential should be offered, particularly to owners with clinically ill pets.
- All dogs and cats should be vaccinated for rabies.
- Dogs and cats should be routinely administered drugs that kill hookworms and roundworms.
- Flea and tick control should be maintained at all
- Veterinary clinic staff members should teach owners techniques to avoid being bitten or scratched.

still common; an estimated 3 million to 6 million people in the United States are infected with Toxocara larva migrans each year, and the average seroprevalence of antibodies against Toxocara is 3.5% in the general human population (Schantz, 1989). These common roundworms are passed as eggs in feces. The eggs larvate and become infectious after 1 to 3 weeks and can survive in the environment for months. Humans are infected after ingesting larvated eggs. Dogs are considered more of a significant problem than cats for the spread of eggs. However, areas such as children's sandboxes may be contaminated with T. cati because of the defecation habits of cats. Human infection after direct contact with dogs or cats is extremely unlikely because the eggs are not immediately infectious.

Dogs and cats can be subclinically affected or may develop poor haircoats, poor weight gain, and gastrointestinal signs. After ingestion of infectious eggs, larvae penetrate the intes-



# BOX 100-2

# General Guidelines for Pet Owners to Avoid Zoonotic Transfer of Disease

- If a new pet is to be adopted, the dog or cat least likely to be a zoonotic risk is a clinically normal, arthropodfree, adult animal from a private family.
- Once the animal to be adopted is identified, it should be quarantined from any immunocompromised person until a thorough physical examination and zoonoses risk assessment is performed by a veterinarian.
- Veterinary care should be sought for all clinically ill
- Physical examination and fecal examination should be performed at least once or twice yearly.
- Fecal material produced in the home environment should be removed daily, preferably by someone other than an immunocompromised individual.
- Use litterbox liners and periodically clean the litterbox with scalding water and detergent.
- Do not allow dogs or cats to drink from the toilet.
- Wear gloves when gardening and wash hands thoroughly when finished.
- Filter or boil water from sources in the environment.
- Wash your hands after handling animals.
- Do not handle animals that you are unfamiliar with.
- Clinically ill animals should not be handled by immunocompromised people, if possible.
- Pets should be maintained within the home environment to lessen exposure to other animals that may carry zoonotic agents, exposure to excrement of other animals, and exposure to fleas and ticks.
- Pets should only be fed commercially processed food.
- People should not share food utensils with pets.
- Avoid being licked by animals.
- Claws of cats should be clipped frequently to lessen the risk of skin penetration.
- To lessen the risk of bites and scratches, do not tease or physically restrain dogs and cats.
- If bitten or scratched by a dog or cat, seek medical
- Control potential transport hosts, such as flies and cockroaches, that may bring zoonotic agents into the
- Cook meat for human consumption to 80°C for 15 minutes minimum (medium-well).
- Wear gloves when handling meat and wash hands thoroughly with soap and water when finished.

tinal wall and migrate through the tissues. Eosinophilic granulomatous reactions involving the skin, lungs, central nervous system (CNS), or eyes then occur, potentially leading to clinical signs of disease. Clinical signs and physical examination abnormalities in affected individuals include skin rash, fever, failure to thrive, CNS signs, cough, pulmonary infiltrates, and hepatosplenomegaly. Peripheral eosinophilia is common. Ocular larva migrans most commonly involves the retina and can cause reduced vision; uveitis and



TABLE 100-1

Prevalence of Enteric Zoonoses in Dogs and Cats in the United States

	ADULT DOGS (N = 130)*	ADULT CATS (N = 263)†	CATS <1 YR (N = 206);	
	0.00/	0.00/	A 09/	
Ancylostoma spp.	0.8%	0.0%	0.0%	
Campylobacter spp.	0.8%	1.0%	0.8%	
Cryptosporidium spp.	3.8%	5.4%	3.8%	
Giardia spp.	5.4%	2.4%	7.2%	
Salmonella spp.	2.3%	1.0%	0.8%	
Toxocara canis	3.1%	0.0%	0.0%	
Toxocara cati	0.0%	3.9%	32.7%	
Toxoplasma gondii	0.0%	0.0%	1.1%	
Any zoonotic agent	14.6%	13.1%	40.7%	

<sup>\*</sup>Colorado dogs (Hackett and Lappin, 2002).

<sup>†</sup> Colorado cats (Hill et al., 2000). ‡ New York State kittens (Spain et al., 2001).



TABLE 100-2

**Characteristics of Common Enteric Zoonoses** 

ORGANISM	SPECIES	INCUBATION
Bacterial		
Campylobacter jejuni	В	Immediately infectious
Escherichia coli	B	Immediately infectious
Helicobacter spp.*	В	Immediately infectious
Salmonella spp.	В	Immediately infectious
Yersinia enterocolitica	В	Immediately infectious
Parasitic Amoeba		
Entamoeba histolytica	D	Cysts are immediately infectious
Parasitic Cestodes		
Echinococcus multilocularis	С	Ova are immediately infectious
Echinococcus granulosa	D	Ova are immediately infectious
Multiceps multiceps	D	Ova are immediately infectious
Parasitic Coccidians		
Cryptosporidium spp.	В	Oocysts are immediately infectious
Toxoplasma gondii	С	Oocysts are infectious after 1-5 day incubation/exposure from environment
Parasitic Flagellates		
Giardia spp.	В	Cysts are immediately infectious
Parasitic Helminths		
Ancylostoma spp.	В	Larva infectious after a more than 3-day incubation/exposure from environment Skin penetration from larva in environment
Baylisascaris procyanosis	D	Larvated ova infectious after 1-3 week incubation/exposure from environment
Strongyloides stercoralis	В	Larvae immediately infectious
Toxocara canis	D	Larvated ova infectious after 1- to 3-week incubation/exposure from environment
Toxocara cati	С	As for T. canis
Uncinaria stenocephala	В	As for Ancylostoma spp.

D, Dog; C, cat; B, dog and cat.
\* Zoonotic potential undetermined; dogs are rarely infected by the ciliate Balantidium coli.

endophthalmitis can also occur. Visceral larva migrans is most common in children between 1 and 4 years of age, whereas ocular larva migrans is most common in older children. Diagnosis in human beings is confirmed by biopsy or can be presumed in cases with classic clinical manifestations, eosinophilia, and positive serology.

Ancylostoma caninum, Ancylostoma braziliense, Ancylostoma tubaeformis, Uncinaria stenocephala, and Strongyloides stercoralis have been associated with cutaneous larva migrans in the United States. After the passage of hookworm eggs into the environment in feces, infectious larvae are released after incubating for 1 to 3 days; humans are infected by skin penetration. In addition, eosinophilic enteritis in humans was reported after ingestion of larvated A. caninum eggs.

Animals are either subclinically ill or have nonspecific signs such as poor haircoats, failure to gain weight, vomiting, or diarrhea. Heavily infected puppies and kittens may have pale mucous membranes from blood loss anemia. In humans the larvae cannot penetrate the dermoepidermal junction and usually die in the epidermis. Clinical signs are related to migration of the larvae, which results in an erythematous, pruritic cutaneous tunnel. Cutaneous signs usually resolve within several weeks. Abdominal pain is the most common clinical sign in humans with *A. caninum* intestinal infection.

*Trichuris vulpis*, the dog whipworm, is most commonly associated with large-bowel diarrhea in dogs. The organism has been detected in feces in some people and has rarely been associated with gastrointestinal signs of disease (Dunn 2002).

Prevention of hookworms and roundworms is achieved by control of animal excrement in human environments. All puppies and kittens should have a fecal flotation performed and should be routinely treated with an anthelmintic that has efficacy against roundworms and hookworms. The Companion Animal Parasite Council (http://www.capcvet. org) recommends that puppies and their mothers be treated at 2, 4, 6, and 8 weeks of age and that kittens and their mothers be treated at 6, 8, and 10 weeks of age. These guidelines are particularly important for areas and animals with heavy parasite burdens. If the puppies and kittens are not presented to the veterinary clinic until vaccination age or are from areas with low prevalence rates for infection, I administer an appropriate anthelmintic such as pyrantel pamoate at each vaccination appointment. Roundworm and hookworm infections are occasionally occult, so all puppies or kittens should receive an anthelmintic whether or not eggs are detected on microscopic examination of feces. In most areas of the country monthly deworming should be considered. Administration of heartworm preventatives that also control hookworms and roundworms is an easy way to provide strategic deworming year-round.

#### **CESTODES**

Dipylidium caninum, Echinococcus granulosa, and Echinococcus multilocularis are cestodes that can infect humans. Wild carnivores are more common definitive hosts of Echinococcus spp. and shed infective eggs into the environment. E. granulosa eggs can be transmitted in feces of dogs after inges-

tion of infected sheep or rabbit tissues; E. multilocularis can be transmitted in feces of dogs or cats after ingestion of an infected rodent. Transmission to humans occurs after ingestion of the intermediate host (flea, Dipylidium) or eggs (Echinococcus spp.). Infection of dogs and cats with cestodes is generally subclinical. Dipylidium infection is most common in children and can lead to diarrhea and pruritus ani. In humans, after ingestion of eggs, which are immediately infectious, Echinococcus enters the portal circulation and spreads throughout the liver and other tissues. E. multilocularis is most common in the northern and central parts of North America but seems to be spreading with the fox population (most common definitive host). Prevention or control of cestodes is based on sanitation procedures and use of taeniacides. Praziquantel is labeled for the treatment of Echinococcus spp. Restricting hunting behavior of dogs and cats and feeding only processed or cooked foods should lessen potential exposure to Echinococcus spp. Monthly administration of praziquantel should be considered in dogs and cats allowed to hunt in endemic areas. Flea control should be maintained to lessen risk of D. caninum infection.

#### COCCIDIANS

Cryptosporidium spp. inhabit the respiratory and intestinal epithelium of many vertebrates, including birds, mammals, reptiles, and fish. Once thought to be a commensal, Cryptosporidium spp. are now known to cause gastrointestinal tract disease in several mammalian species, including rodents, dogs, cats, calves, and humans. The organisms have an enteric life cycle similar to that of other coccidians that culminates in the production of thin-walled, autoinfective oocysts and thick-walled, environmentally resistant oocysts that are passed in feces (Fig. 100-1). Oocysts (4 to 6 µm in diameter) are passed sporulated and are immediately infectious to other hosts. Multiple species of Cryptosporidium spp. exist, including C. parvum, C. hominis, C. felis, and C. canis. Although some Cryptosporidium infect multiple animal

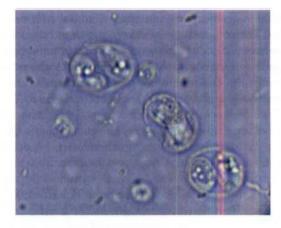


FIG 100-1
Cryptosporidium parvum and Toxoplasma gondii oocysts on a fecal flotation. The C. parvum oocysts are approximately 4 × 5 µm, and the T. gondii oocysts are approximately 10 × 12 µm.

species, others have a limited host range. However, strains that infect both pets and people cannot be differentiated by light microscopy from those that infect only pets, so all *Cryptosporidium* spp. should be considered potentially zoonotic. The most common *Cryptosporidium* spp. isolated from dogs and cats are the host-adapted *C. canis* and *C. felis*, respectively.

The prevalence of *Cryptosporidium* spp. oocysts in dog and cat feces approximates that of *Giardia* (see Table 100-1), leading to the recommendation that all dogs or cats with diarrhea in the homes of immunosuppressed people be assessed for this infection. In the United States the seroprevalence of immunoglobulin G (IgG) antibodies in serum is 8.6% in cats and up to 58% in humans. In dogs and cats with diarrhea, *Cryptosporidium* spp. DNA was amplified from feces of 16.8% and 29%, respectively (Scorza et al., 2006). These results suggest that exposure to *Cryptosporidium* spp. is quite common in pets and people.

Person-to-person contact with oocysts by fecal-oral contamination and ingestion of contaminated water are the most likely routes of exposure. *C. parvum* infection of humans after exposure to infected calves has been recognized for years. Human infection associated with contact with infected dogs and cats has been reported but is thought to be unusual. In one study cat or dog ownership was not statistically associated with cryptosporidiosis in human immunodeficiency virus (HIV)-infected people (Glaser et al., 1999).

Infection of dogs and cats by *Cryptosporidium* spp. is usually subclinical, but small-bowel diarrhea occurs in some cases. Immunosuppression may potentiate disease; several dogs and cats had concurrent feline leukemia virus infection, canine distemper virus infection, or intestinal lymphoma. Clinical cryptosporidiosis is characterized by small-bowel diarrhea and is generally self-limiting in immunocompetent people, but fatal infection is common in those with AIDS. From 10% to 20% of humans with AIDS will be infected by *C. parvum* during the course of their illness.

The small size (approximately 4 to 6 µm in diameter) of Cryptosporidium spp. oocysts leads to difficulty in diagnosis. Routine salt solution flotation and microscopic examination at ×100 magnification commonly lead to false-negative results. The combination of concentration techniques with fluorescent antibody staining or acid-fast staining appears to be more sensitive. Multiple enzyme-linked immunosorbent assays for the detection of C. parvum antigen in feces are commercially available but do not accurately detect C. felis or C. canis. Polymerase chain reaction (PCR) is the most sensitive test to date, but assays are not routinely available and are not standardized among laboratories. No drug has been shown to eliminate Cryptosporidium spp. from the gastrointestinal tract. However, clinical signs usually resolve when azithromycin is administered orally at 10 mg/kg/day, tylosin is administered orally at 10 to 15 mg/kg three times a day, or paromomycin is administered orally at 150 mg/kg daily. Paromomycin has been associated with renal insufficiency and so should never be administered to animals with blood in the feces, which appears to allow for the absorption of this aminoglycoside. Optimal duration of therapy is

unknown; some cases have required administration of azithromycin for several weeks before clinical signs resolve. Avoiding exposure is the most effective prevention. Routine disinfectants require extremely long contact with the organism to be effective. Drying, freeze thawing, and steam cleaning can inactivate the organism. Surface water collected in the field for drinking should be boiled or filtered.

Toxoplasma gondii is an ubiquitous coccidian with worldwide distribution. Most seroprevalence studies performed in the United States suggest that at least 30% of cats and humans have previously been exposed. Cats are the only known definitive host of the organism, and they complete the enteroepithelial cycle (sexual phase) that results in the passage of environmentally resistant unsporulated oocysts in feces. Oocyst sporulation occurs in 1 to 5 days in the presence of oxygen; sporulated oocysts are infectious to most warmblooded vertebrates (see Fig. 100-1). After infection by T. gondii, an extraintestinal phase that ultimately leads to the formation of tissue cysts containing the organism develops. Infection by T. gondii occurs after ingestion of sporulated oocysts, after ingestion of tissue cysts, or transplacentally. Transplacental infection of humans and cats usually occurs only if the mother is infected for the first time during gestation.

In dogs and cats, clinical disease from T. gondii infection occurs occasionally and is manifested most commonly by fever, uveitis, pulmonary disease, hepatic disease, and CNS disease (see Chapter 99). Infected immunocompetent humans are generally asymptomatic; self-limiting fever, lymphadenopathy, and malaise occur occasionally. Transplacental infection of humans results in clinical manifestations, including stillbirth, hydrocephalus, hepatosplenomegaly, and retinochoroiditis. Presence of T. gondii antibodies has been associated with presence of behavioral abnormalities in people, but a direct cause and effect has not be established. Chronic tissue infection in humans can be reactivated by immunosuppression, leading to dissemination and severe clinical illness; this has been commonly associated with drug-induced immunosuppression and AIDS. Approximately 10% of humans with AIDS develop toxoplasmic encephalitis. Oocysts are most effectively demonstrated in cat feces after sugar solution centrifugation. Clinical toxoplasmosis is difficult to diagnose in humans, dogs, and cats but usually involves the combination of clinical signs, serologic test results, organism demonstration techniques, and response to anti-Toxoplasma drugs (see Chapter 99).

Although *T. gondii* is recognized as one of the most common zoonoses, humans are usually not infected by direct contact with cats. The oocyst shedding period usually lasts several days to several weeks (approximately 7 to 10 days if the cat was infected by tissue cyst ingestion). Because oocysts have to sporulate to be infectious, contact with fresh feces cannot cause infection. Cats are quite fastidious and usually do not allow feces to remain on their skin for periods long enough to lead to oocyst sporulation. Oocysts were not isolated from the fur of cats 7 days after completion of the oocyst shedding period. No association between cat owner-

ship and *T. gondii* seroprevalence was demonstrated in a group of HIV-infected humans (Wallace et al., 1999). In most studies veterinary health care providers do not have an increased incidence of toxoplasmosis compared with the general population. Cats do not need to be removed from households with immunodeficient people or pregnant women because of the risk for acquiring toxoplasmosis (http://www.cdc.gov/ncidod/dpd/parasites/toxoplasmosis/ToxoWomen.pdf). Prevention of *T. gondii* infection is summarized in Box 99-1.

# FLAGELLATES, AMOEBA, AND CILIATES

Giardia spp. (flagellate), Entamoeba histolytica (amoeba), and Balantidium coli (ciliate) are enteric protozoans that can be transmitted to humans by contact with feces; the cysts do not require an incubation period to become infectious. E. histolytica infection is extremely rare in dogs and cats; B. coli infection is rare in dogs and has never been reported in cats.

Giardia spp. infection of dogs and cats is common and can be detected in feces of normal dogs and cats and in those with small-bowel diarrhea (and occasionally mixed-bowel diarrhea in cats). Clinical signs of disease are generally more severe in immunodeficient individuals. Because the organism is immediately infectious when passed as cysts in stool, direct zoonotic transfer is possible. Genetic studies have detected multiple Giardia spp., and most dogs and cats are infected with the host-adapted assemblages C, D, and F. However, as is the case with Cryptosporidium, because determining zoonotic strains of Giardia spp. by microscopic examination is not possible, assume that feces from all dogs and cats infected with Giardia spp. are a potential human health risk.

Fecal examination should be performed on all dogs and cats at least yearly, and treatment with drugs with anti-Giardia activity, such as fenbendazole, metronidazole, or febantel/ praziquantel/pyrantel, should be administered if indicated (see Chapter 30). Centrifugation techniques (zinc sulfate or sugar) are considered by most parasitologists to be optimal for demonstration of cysts (see Fig. 92-3). If fresh stool is available from dogs or cats with diarrhea, examination of a wet mount to detect the motile trophozoites may improve sensitivity. Monoclonal antibody-based immunofluorescent antibody tests, fecal antigen tests, and PCR assays are available but should be used in addition to, not in lieu of, fecal flotation, which can also reveal other parasites.

Giardia vaccines for subcutaneous administration are now available for both dogs and cats (see Chapter 94). The Giardia vaccines are not currently recommended for routine prophylactic use in cats or dogs, but vaccination against Giardia could be considered in cats or dogs with recurrent infection as immunotherapy. Prevention of zoonotic giardiasis includes boiling or filtering surface water for drinking and washing hands that have handled fecally contaminated material, even if gloves were worn. In dogs and cats treated for giardiasis, infection can be documented again several weeks later in approximately 25% of animals. Thus the primary goal for the treatment of giardiasis is elimination of

diarrhea. Whether these cases are a treatment failure or a reinfection is unknown.

#### **BACTERIA**

Salmonella spp., Campylobacter spp., Escherichia coli, Yersinia enterocolitica, and Helicobacter spp. each infect dogs and cats and can cause disease in humans. Transmission from animals to humans is by fecal-oral contact. Dogs can be subclinical carriers of Shigella spp., but humans are the natural hosts. Although Helicobacter pylori was isolated from a colony of cats, whether dogs and cats are a common source of Helicobacter infection in humans is unclear. However, on the basis of epidemiologic studies, it is unlikely. In three recent prevalence studies of enteric zoonoses, Salmonella spp. and Campylobacter spp. infections were uncommon in pet dogs and cats (see Table 100-1). The prevalence of Salmonella and Campylobacter infections is greater in young animals housed in unsanitary or crowded environments.

Gastroenteritis can occur in dogs or cats after infection by Salmonella spp., Campylobacter spp., or F. coli; Y. enterocolitica is probably a commensal agent in animals but causes fever, abdominal pain, polyarthritis, and bacteremia in humans. Helicobacter infections cause gastritis, which is commonly manifested as vomiting, belching, and pica. Salmonella spp. infection in dogs and cats is often subclinical. Approximately 50% of clinically affected cats have gastroenteritis; many are presented with signs of bacteremia. Salmonellosis of cats and humans has been associated with songbirds (songbird fever). Abortion, stillbirth, and neonatal death can result from in utero infection. Diagnosis of Salmonella spp., Campylobacter jejuni, E. coli, and Y. enterocolitica is based on culture of feces (see Chapter 92). A single negative culture may not rule out infection. Rectal cytology (see Chapter 92) should be performed on all animals with diarrhea. If neutrophils are noted, culture for enteric bacteria is indicated, particularly if the animal is owned by an immunodeficient individual.

Antibiotic therapy can control clinical signs of disease from infection by Salmonella spp. or Campylobacter spp. (see Chapter 30) but should not be administered orally to animals that are subclinical carriers of Salmonella because of the risk for antibiotic resistance. Strains of Salmonella resistant to most antibiotics have been detected in several cats. Prevention of enteric bacterial zoonoses is based on sanitation and control of exposure to feces. Immunodeficient people should avoid young animals and animals from crowded or unsanitary housing, particularly if clinical signs of gastrointestinal tract disease are occurring.

# BITE, SCRATCH, OR EXUDATE EXPOSURE ZOONOSES

## **BACTERIA**

Approximately 300,000 emergency room visits per year in the United States are made by people bitten by animals. Most of the aerobic and anaerobic bacteria associated with bite or scratch wounds cause only local infection in immunocompetent individuals. However, 28% to 80% of cat bites become infected, and severe sequelae, including meningitis, endocarditis, septic arthritis, osteoarthritis, and septic shock, can occur. The majority of the aerobic and anaerobic bacteria associated with dog or cat bite or scratch wounds lead only to local infection in immunocompetent individuals. Immunodeficient humans or those exposed to *Pasteurella* spp., *Capnocytophaga canimorsus* (DF-2), or *Capnocytophaga cynodegmi* more consistently develop systemic clinical illness. Splenectomized humans are at increased risk for developing bacteremia. *Pasteurella multocida* from a cat was cultured from the lungs of a man with AIDS who had only passive contact with the cat.

Dogs and cats are subclinical carriers of multiple bacteria in the oral cavity. After a person is bitten or scratched, local cellulitis is noted initially, followed by evidence of deeper tissue infection. Bacteremia and the associated clinical signs of fever, malaise, and weakness are common, and death can occur within hours after infection with *Capnocytophaga* spp. in immunodeficient or splenectomized humans. Diagnosis is confirmed by culture. Treatment of carrier animals is not needed. Treatment of clinically affected humans includes local wound management and parenteral antibiotic therapy. Penicillin derivatives are highly effective against most *Pasteurella* infections; penicillins and cephalosporins are effective against *Capnocytophaga* spp. in vitro.

Mycoplasma spp. infections of humans resulting from cat bites, one with cellulitis and one with septic arthritis, have been reported. L-form bacteria are cell wall-deficient organisms associated with chronic draining skin wounds in cats that are commonly resistant to cell wall-inhibiting antibiotics, such as penicillins and cephalosporins. Infection of a human being after a cat bite has been documented. Diagnosis can be confirmed only by histologic examination of tissue. Doxycycline has been used to treat cats and people successfully. Gloves should be worn when attending cats with draining tracts, and hands should be cleansed thoroughly.

Bartonella henselae can infect both dogs and cats and is the most common cause of cat scratch disease as well as bacillary angiomatosis and bacillary peliosis-common disorders in humans with AIDS (Table 100-3). Dogs and cats can also be infected with several other Bartonella spp., including B. clarridgeiae, B. koehlerae, B. vinsonii (dogs), and B. quintana (see Chapter 95). B. henselae has been isolated from the blood of subclinically ill, seropositive cats and also from some cats with a variety of clinical manifestations such as fever, lethargy, lymphadenopathy, uveitis, gingivitis, and neurologic diseases. Infection of dogs has also been associated with clinical illness. Seroprevalence in cats varies by region, but as many as 93% of cats in some geographic areas of the United States are Bartonella spp. seropositive. Both B. henselae and B. clarridgeiae are transmitted between cats by fleas, so the prevalence is greatest in cats from states where fleas are common (Lappin et al., 2006). Transmission to humans commonly occurs after cat bites or scratches; the disease appears to be transmitted most commonly from



TABLE 100-3

Selected Canine or Feline Zoonoses Associated with Bites, Scratches, or Contact with Exudates

ORGANISM	SPECIES	CLINICAL DISEASE
Bacterial		
Bartonella spp.	С	Cat: subclinical, fever, uveitis, gingivitis, lymphadenopathy, neurological disease
		Human being: fever, malaise, lymphadenopathy, bacillary angiomatosis, bacillary peliosis
Capnocytophaga canimorsus	В	Dog and cat: subclinical oral carriage Human being: bacteremia
Francisella tularensis	С	Cat: septicemia, pneumonia
		Human being: ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of infection)
Yersinia pestis	С	Cat: bubonic, bacteremic, or pneumonic
		Human: bubonic, bacteremic, or pneumonic
fungal		
Dermatophytes	В	Dog, cat, and human: superficial dermatologic disease
Sporothrix schenkii	C	Cat: chronic draining cutaneous tracts
		Human being: chronic draining cutaneous tracts
Viral		
Rabies	В	Dog and cat: progressive CNS disease
		Human: progressive CNS disease

kittens. *B. henselae* survives in flea feces for days, so the cat's claws and teeth are likely contaminated with *B. henselae* during grooming, which emphasizes the maintenance of flea control on dogs and cats.

Humans with cat scratch disease develop a variety of clinical signs, such as lymphadenopathy, fever, malaise, weight loss, myalgia, headache, conjunctivitis, skin eruptions, and arthralgia. Bacillary angiomatosis is a diffuse disease resulting in vascular cutaneous eruptions. Bacillary peliosis is a diffuse systemic vasculitis of parenchymal organs, particularly the liver. The incubation period for cat scratch disease is approximately 3 weeks. Most cases of cat scratch disease are self-limiting but may take several months to completely resolve.

Blood culture, blood PCR, and serologic testing can be used to determine the risk of individual cats (see Chapter 95). However, although serologic testing can be used to determine whether an individual cat has been exposed, both seropositive and seronegative cats can be bacteremic, limiting the diagnostic utility of serologic testing. Thus testing healthy cats for *Bartonella* spp. infection is not currently recommended by the Centers for Disease Control and Prevention or the American Association of Feline Practitioners (Brunt et al., 2006). Testing should be reserved for cats with suspected clinical bartonellosis.

In experimental studies, administration of doxycycline, tetracycline, erythromycin, amoxicillin-clavulanate, or enrofloxacin can limit bacteremia but does not cure infection in all cats and has not been shown to lessen the risk of cat scratch disease. Azithromycin is commonly administered to cats with suspected clinical bartonellosis, but no published data document clearance of infection in cats. Thus antibiotic treatment of healthy bacteremic cats is controversial and not currently recommended by the Centers for Disease Control and Prevention or the American Association of Feline Practitioners (Brunt et al., 2006). Treatment should be reserved for cats with suspected clinical bartonellosis. Strict flea control should be maintained. Kittens should be avoided by immunodeficient people. Cat claws should be kept clipped, and cats should never be teased. Cat-induced wounds should immediately be cleansed, and medical advice sought.

Feline plague is caused by Yersinia pestis, a gram-negative coccobacillus found most commonly in Midwestern and far Western states, particularly New Mexico and Colorado. Rodents are the natural hosts for this bacterium; cats are most commonly infected by ingestion of bacteremic rodents or lagomorphs or by being bitten by Yersinia-infected rodent fleas. Dogs are more resistant to infection and have not been associated with zoonotic transfer. Humans are most commonly infected by rodent flea bites, but many cases of transmission by exposure to wild animals and infected domestic cats have been documented. From 1977 to 1998, 23 cases of human plague (7.7% of the total cases) resulted from contact with infected cats. Infection can be induced by inhalation of respiratory secretions of cats with pneumonic plague, through bite wounds, or by contamination of mucous membranes or abraded skin with secretions or exudates.

Bubonic, septicemic, and pneumonic plague can develop in cats and humans; each form has accompanying fever, headache, weakness, and malaise. Because cats are most commonly infected by ingestion of bacteremic rodents, suppurative lymphadenitis (buboes) of the cervical and submandibular lymph nodes is the most common clinical manifestation. Exudates from cats with lymphadenopathy should be examined cytologically for the presence of large numbers of the characteristic bipolar rods (see Fig. 95-2). The diagnosis is confirmed by fluorescent antibody staining of exudates; culture of exudates, the tonsillar area, and saliva; and documentation of increasing antibody titers. People who are exposed to infected cats should be urgently referred to physicians for antimicrobial therapy, and public health officials should be alerted. Doxycycline, enrofloxacin, chloramphenicol, or aminoglycosides can be used successfully for the treatment of plague. Parenteral antibiotics should be used during the bacteremic phase. Drainage of lymph nodes may be required. Cats with suppurative lymphadenitis should be considered plague suspects, and extreme caution should be exercised when handling exudates or treating draining wounds. Suspect animals should be treated for fleas and housed in isolation. Cats are generally not considered infectious to humans after 4 days of antibiotic treatment.

Francisella tularensis is the gram-negative bacillus found throughout the continental United States that causes tularemia. Dermacentor variabilis (American dog tick), Dermacentor andersoni (American wood tick), and Amblyomma americanum (Lone Star tick) are known vectors. Human tularemia occurs most commonly after exposure to ticks and less commonly from contact with infected animals. There have been at least 51 cases of human tularemia resulting from contact with infected cats. Dogs are not considered a source of human tularemia but may facilitate human exposure by bringing infected ticks into the environment. Cats are infected most frequently by tick bites or ingestion of infected rabbits or rodents. Most cases of feline tularemia have been documented in the Midwest, particularly Oklahoma. However, a recent study reported a seroprevalence of 12% in cats in a same sample set (n = 91) in the Northeast (Magnarelli et al., 2007)

Infected cats exhibit generalized lymphadenopathy and abscess formation in organs such as the liver and spleen, which leads to fever, anorexia, icterus, and death. Ulceroglandular, oculoglandular, glandular, oropharyngeal, pneumonic, and typhoidal forms have been described in humans and develop depending on the route of exposure. Unlike the situation with plague, the organism is not often recognized in exudates or lymph node aspirates from infected cats. Cultures and documentation of increasing antibody titers can be used to confirm the diagnosis in cats and humans. Most cases of tularemia in cats have been diagnosed at necropsy, so optimal treatment is unknown. Streptomycin and gentamicin are the drugs used most commonly to treat humans. Tetracycline or chloramphenicol can be used in cases not requiring hospitalization but may be associated with relapses.

The disease is prevented by avoiding exposure to lagomorphs, ticks, and infected cats. All cats dying with bacteremia should be handled carefully.

#### **FUNGI**

Of the many fungal agents that infect both humans and animals, only *Sporothrix schenckii* and the dermatophytes have been shown to infect humans on direct exposure. *Histoplasma, Blastomyces, Coccidioides, Aspergillus,* and *Cryptococcus* infections of humans and animals can occur in the same household but generally result from a common environmental exposure (see Chapter 98).

Sporothrix is cosmopolitan in distribution, and the soil is believed to be the natural reservoir. Infection of cats and humans usually occurs after the organism contaminates broken skin. Cats are believed to be infected by scratches from contaminated claws of other cats; infection is most common in outdoor males. Humans can be infected by contamination of cutaneous wounds with exudates from infected cats. Sporothrix infection in cats can be cutaneolymphatic, cutaneous, or disseminated. Chronic draining cutaneous tracts are common. Cats commonly produce large numbers of the organism in feces, tissues, and exudates; thus veterinary care personnel are at high risk when treating infected cats (Fig. 100-2). The clinical disease in humans is similar to that in cats. Dogs generally do not produce large numbers of Sporothrix in exudates, so they are less of a zoonotic risk. The organism can be demonstrated by cytologic examination of exudates or culture. Fluconazole, itraconazole, or ketoconazole are effective treatments. Gloves should be worn when attending cats with draining tracts, and hands should be cleansed thoroughly.

#### **VIRUSES**

Rabies is still the only significant small animal viral zoonosis in the United States. See Chapter 69 for a discussion of this agent.

Pseudorabies is a herpesvirus that infects pigs; dogs and humans can develop self-limiting pruritic skin disease after

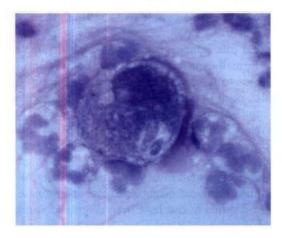


FIG 100-2 Sporothrix schenckii in a macrophage from an infected cat. Two rod-shaped organisms are visible in the cytoplasm.

exposure. Dogs occasionally develop CNS disease characterized by depression and seizures. Diagnosis is suspected on the basis of the exposure history, and prevention is by avoiding exposure.

Some authorities have been concerned whether the retroviruses of cats—feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and feline foamy virus (FeFV)—can infect humans because FeLV subtypes B and C can replicate in human cell lines. However, to date humans have not been shown to be infected with any of the feline retroviruses. In the most recent study 204 veterinarians and others potentially exposed to feline retroviruses were assessed for antibodies against FIV and FeFV, FeLV p27 antigen, and FeLV provirus; test results on all were negative (Butera et al., 2000). Because both FeLV and FIV can induce immune deficiency, infected cats should be considered more likely than retrovirus-naïve cats to be carrying other potential zoonotic agents, particularly if gastrointestinal tract signs are present.

# RESPIRATORY TRACT AND OCULAR ZOONOSES

#### **BACTERIA**

Bordetella bronchiseptica is a bacterium that induces respiratory tract infections in dogs and cats (see Chapter 21). The classic clinical manifestation is tracheobronchitis, but the organism can also cause pneumonia, sneezing, and nasal discharge. Humans rarely develop clinical disease caused by B. bronchiseptica unless they are immunologically compromised (Table 100-4). Only 39 cases of B. bronchiseptica infection in humans had been reported by 1998; most of these patients were immunodeficient. Association with a cat has only been reported once, in a person coinfected with HIV and B. bronchiseptica. Amoxicillin-clavulanate, chloramphenicol, enrofloxacin, and tetracycline derivatives are all effective treatments. Animals with upper or lower respiratory tract inflammatory disease should be kept away from immunodeficient people until the animals are clinically normal. However, treated animals can still shed the organism.

Chlamydophila felis (formerly Chlamydia psittaci) causes mild conjunctival disease and rhinitis in cats (Table 100-4). In Japan the prevalence rates of antibodies against an isolate of C. felis were 51.1% in stray cats, 15.0% in pet cats, 3.1% in the general human population, and 5.0% in small animal clinic veterinarians, suggesting that transfer between cats and humans may occur (Yan et al., 2000). Conjunctivitis in humans after direct contact with ocular discharges from cats has been described. A human isolate of Chlamydia spp. was inoculated into cats, resulting in conjunctivitis and persistent infection, suggesting that the isolate was a feline strain. Occasionally the organism is associated with systemic disease; atypical pneumonia was diagnosed in an apparently immunocompetent 48-year-old man, malaise and cough were diagnosed in an immunosuppressed woman, and endocarditis and glomerulonephritis were diagnosed in a 40-year-

# **TABLE 100-4**

Selected Canine or Feline Zoonoses Associated with Respiratory or Ocular Secretions of Dogs or Cats

ORGANISM	SPECIES	CLINICAL SIGNS
Bordetella bronchiseptica*	В	Dog and cat: upper respiratory, rarely pneumonia Immunosuppressed humans: pneumonia
Chlamydophyla felis*	С	Cat: conjunctivitis, mild upper respiratory Human being: conjunctivitis
Francisella tularensis	С	Cat: septicemia, pneumonia  Human being: ulceroglandular, oculoglandular, glandular, pneumonic, or typhoidal (depending on route of infection)
Streptococcus group A†	В	Dog and cat: subclinical, transient carrier Human being: "strep throat," septicemia
Yersinia pestis	С	Cat: bubonic, bacteremic, or pneumonic Human being: bubonic, bacteremic, or pneumonic

D, Dog; C, cat; B, dog and cat.

old woman. Diagnosis is based on organism demonstration by culture, cytologic documentation of characteristic inclusion bodies, or fluorescent antibody staining of conjunctival scrapings. Tetracycline or chloramphenicol-containing eye ointments generally are effective in the treatment of infection. Oral administration of doxycycline is still considered the optimal way to clear the carrier state. Care should be taken to avoid direct conjunctival contact with discharges from the respiratory or ocular secretions of cats, especially by immunosuppressed persons (see Box 100-2). Employees should be directed to wear gloves or wash hands carefully when attending cats with conjunctivitis.

Nosocomial spread of methicillin-resistant Staphylococcus aureus (MRSA) among veterinary or human patients and doctors was recently recognized as a significant problem in hospitals; MRSA should now also be considered a zoonotic agent (Weese et al., 2006).

Humans are the principal natural hosts for Streptococcus group A bacteria, Streptococcus pyogenes, and Streptococcus pneumoniae, which cause "strep throat" in humans. Dogs and cats in close contact with infected humans can develop transient, subclinical colonization of pharyngeal tissues and can transmit the infection to other humans. However, this is poorly documented and believed to be unusual. The organism can be cultured from the tonsillar crypts. Culture-positive animals should be treated with penicillin derivatives. If animals are to be treated in a household with chronic, recurrent strep throat, all humans should also be treated because they also could be chronic subclinical carriers.

Yersinia pestis and Francisella tularensis can be transmitted from cats to humans in respiratory secretions. In endemic areas, cats with clinical signs or radiographic abnormalities consistent with pneumonia should be handled as plague or tularemia suspects. Gloves, mask, gown, and eye protection should be worn while performing transoral airway washings in suspect cats.

#### VIRUSES

Avian influenza A (H5N1) virus has infected some cats after close exposure to infected birds. In studies of naturally exposed and experimentally infected cats, some cats developed respiratory disease (Thiry ct al., 2007) and others have become asymptomatic carriers (Leschnik et al., 2007). Results of studies assessing transmission between infected cats have been variable. To date, transmission of the infection from cats to humans has not been documented.

# GENITAL AND URINARY TRACT ZOONOSES

Coxiella burnetii is a rickettsial agent found throughout the world, including North America (Table 100-5). Many ticks, including Rhipicephalus sanguineus, are naturally infected with C. burnetii. Cattle, sheep, and goats are commonly subclinically infected and pass the organism into the environment in urine, feces, milk, and parturient discharges. Seropositive dogs have been detected, but zoonotic transfer to humans from dogs has not been documented. Infection of cats most commonly occurs after tick exposure, ingestion of contaminated carcasses, or aerosolization from a contaminated environment. Fever, anorexia, and lethargy developed in some experimentally infected cats. Infection has been associated with abortion in cats, but the organism can also be isolated from normal parturient cats. Infection of cats appears to be common; 20% of cats from a shelter in southern California and 20% of cats in Maritime Canada were seropositive, the organism was grown from the vagina of healthy cats in Japan (Nagaoka et al., 1998), and DNA of the organism was amplified from uterine tissues of cats in Colorado (Cairns et al., 2006).

Human illness associated with direct contact with infected cats occurs after aerosol exposure to the organism passed by

<sup>\*</sup> Zoonotic potential largely unknown.

<sup>†</sup>Minimal zoonotic potential.



TABLE 100-5

Selected Canine and Feline Zoonoses Associated with Contact with Urine or Genital Secretions

ORGANISM	SPECIES	CLINICAL DISEASE
Bacterial		
Brucella canis	D	Dog: orchitis, epididymitis, abortion, stillbirth, vaginal discharge, uveitis, diskospondylitis, fever, malaise Human: fever, malaise
Leptospira spp.	В*	Dog: fever, malaise, inflammatory urinary tract or hepatic disease, uveitis, CNS disease Human being: fever, malaise, inflammatory urinary tract or hepatic disease, uveitis, CNS disease
Rickettsial		
Coxiella burnetii	С	Cat: subclinical, abortion, or stillbirth Human being: fever, pneumonitis, lymphadenopathy, myalgia, arthritis

D, Dog; C, cat; B, dog and cat, CNS, central nervous system.

parturient or aborting cats; clinical signs develop 4 to 30 days after contact. Humans commonly develop acute clinical signs similar to those associated with other rickettsial discases, including fever, malaise, headache, pneumonitis, myalgia, and arthralgia. After primary infection, chronic Q fever develops in approximately 1% and can manifest as hepatic inflammation or valvular endocarditis. Tetracyclines, chloramphenicol, and quinolones are usually effective therapeutic agents in humans. Gloves and masks should be worn when attending to parturient or aborting cats. People who develop fever or respiratory tract disease after exposure to parturient or aborting cats should seek medical attention.

Leptospira spp. can be transmitted in urine from infected dogs and cats to humans, resulting in clinical disease. Host-adapted species cause subclinical infection; infection by non-host-adapted species commonly results in clinical illness. The organisms enter the body through abraded skin or intact mucous membranes. (See Chapter 95 for a detailed discussion of the clinical manifestations of this disease and its treatment in dogs and cats.) Human clinical syndromes vary with the serovar but are similar to those that occur in the dog. Animals with suspected leptospirosis should be handled while wearing gloves. Contaminated surfaces should be cleaned with detergents and disinfected with iodine-containing products.

Brucella canis is a bacterium that preferentially infects the testicles, prostate, uterus, and vagina of dogs (see Chapter 57 and 62). The infection is maintained in dogs primarily by venereal transmission. Humans can be infected by direct contact with vaginal and preputial discharges from dogs. Clinical syndromes in dogs are diverse but commonly include abortion, stillbirth, failure to conceive, orchitis, epididymitis, vaginal discharge, uveitis, discospondylitis, and bacteremia. Intermittent fever, depression, and malaise are common in infected people. Diagnosis is based on serologic testing or demonstration of the organism by culture. Dogs with clinical signs of brucellosis should be evaluated serologically for Bru-

cella infection with the 2-mercaptoethanol rapid slide agglutination card test. Seronegative dogs are unlikely to harbor *Brucella* unless the clinical syndrome is peracute. Seropositive dogs should have results confirmed by tube agglutination or agar gel immunodiffusion. Long-term antibiotic treatment (tetracyclines, aminoglycosides, quinolones) usually does not clear the infection. Ovariohysterectomy or castration will lessen contamination of the environment. Genital tract secretions should be avoided.

### SHARED VECTOR ZOONOSES

Some zoonotic agents are transmitted between animals and humans by shared vectors such as fleas, ticks, or mosquitoes. Rickettsia rickettsii (ticks), Ehrlichia spp. (ticks), Anaplasma phagocytophilum (ticks), Borrelia burgdorferi (ticks), Rickettsia felis (fleas), Bartonella spp. (fleas and ticks), Dipylidium caninum (fleas), Dirofilaria immitis (mosquitoes), and West Nile virus (mosquitoes) are examples of vector-borne zoonoses common in the United States. For the flea- and tickborne zoonoses, the pet brings the vector of the organism into the environment, resulting in exposure of the human being. Veterinary health care providers could have a slightly increased risk of exposure because they handle many animals infested with fleas and ticks. However, the vector, not direct contact with the infested animal, results in infection of the person. Flea and tick control should always be maintained animals, and infested animals that are seen in the clinic should be treated immediately. See other sections of this text for detailed discussions of these agents.

#### SHARED ENVIRONMENT ZOONOSES

Some agents that infect both animals and man are not commonly transmitted between the pet and the owner by direct

<sup>\*</sup> Cats of minimal significance.

contact but are acquired from the same environmental source. Notable examples include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Aspergillus* spp. See other sections of this text for detailed discussions of these agents.

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# Drugs Used to Treat Infectious Diseases of Dogs and Cats and General Dosing Guidelines\*

DRUG	TRADE NAME	CANINE DOSAGE	FELINE DOSAGE
Antibiotics			
Acetamides			
Chloramphenicol		15-25 mg/kg, q8h, PO, SC, IV, IM	15-25 mg/kg, q12h, PO, SC, IV, IM
Flurfenicol		20 mg/kg, q8h, IM, SC	_
Aminoglycosides			
Amikacin	Amiglyde-V	15-30 mg/kg, q24h, IV, IM, SC	15-20 mg/kg, q24h, IV, IM, SC
Gentamicin		6 mg/kg, q24h, IV, IM, SC	6-8 mg/kg, q24h, IV, IM, SC
Neomycin		22 mg/kg, q8-12h, PO	22 mg/kg, q8-12h, PO
Tobramycin	Nebcin	2 mg/kg, q8h, IV, IM, SC	2 mg/kg, q8h, IV, IM, SC
Carbapenems			
lmipenem	Primaxin	3-10 mg/kg, q6-8h, IV, IM	3-10 mg/kg, q6-8h, IV, IM
Cephalosporins			
Cefadroxil (first generation) Cefpodoxine (third generation) Cephalexin (first generation) Cefazolin (first generation)	Cefa-Tabs	22-35 mg/kg, q12h, PO 5-10 mg/kg, q24h 20-50 mg/kg, q8-12h, PO 20-33 mg/kg, q8-12h, SC, IM, IV	22-35 mg/kg, q24h, PO 5-10 mg/kg, q24h 20-50 mg/kg, q8-12h, PO 20-33 mg/kg, q8-12h, SC, IM, IV
Cefoxitin (second generation)	Mefoxin	15-30 mg/kg, q8h, SC, IM, IV	15-30 mg/kg, q8h, SC, IM, IV
Cefixime (third generation) Cefotaxime (third generation)	Suprax	5-12.5 mg/kg, q12-24h, PO 20-80 mg/kg, q8h, SC, IM, IV	5-12.5 mg/kg, q12-24h, PO 20-80 mg/kg, q8h, SC, IM, IV
Ceftiofur	Naxcel	2.2 mg/kg, q24h, SC	2.2 mg/kg, q24h, SC
Macrolides/lincosamides			
Azithromycin†	Zithromax	5-10 mg/kg, q12-24h, PO	5-15 mg/kg, q24h, PO
Clindamycin	Antirobe	5-20 mg/kg, q12-24h, PO, SC, IM, IV	5-25 mg/kg, q12-24h, PO, SC, IM
Erythromycin		10-25 mg/kg, q8-12h, PO	10-25 mg/kg, q8-12h, PO



# Drugs Used to Treat Infectious Diseases of Dogs and Cats and General Dosing Guidelines\*—cont'd

DRUG	TRADE NAME	CANINE DOSAGE	FELINE DOSAGE
Lincomycin	· ·-	11-22 mg/kg, q12h, PO, IM, IV, SC	11-22 mg/kg, q12h, PO, IM, IV, SC
Tylosin		5-40 mg/kg, q12-24h, PO	5-40 mg/kg, q12-24h, PO
<b>Nitroimidazole</b> Metronidazole‡ Ranidazole	Flagyl	10-30 mg/kg, q8-24h, PO —	10-30 mg/kg, q12-24h, PO 20-30 mg/kg, q12h, PO
Penicillins			
Amoxicillin Amoxicillin clavulanate Ampicillin sodium Carbenicillin Dicloxacin Oxacillin	Clavamox Geocillin Prostaphlin	10-22 mg/kg, q8-12h, PO, SC 12.5-25 mg/kg, q8-12h, PO 20-40 mg/kg, q8h, SC, IM, IV 22-33 mg/kg, q8h, PO 25 mg/kg; q6-8h, PO 22-40 mg/kg, q8h, PO, SC, IM,	10-22 mg/kg, q8-12h, PO, SC 62.5 mg, q8-12h, PO 20-40 mg/kg, q8h, SC, IM, IV 22-33 mg/kg, q8h, PO 25 mg/kg, q6-8h, PO 22-40 mg/kg, q8h, PO, SC, IM,
Penicillin G Ticarcillin		IV 22,000 U/kg, q6-8h, PO, IM, IV 20-50 mg/kg, q6-8h	IV 22,000 U/kg, q6-8h, PO, IM, IV IM, IV, SC
Quinolones			
Ciprofloxacin Difloxacin	Cipro Dicural	10-20 mg/kg, q24h, PO 5-10 mg/kg, q24h, PO	5-15 mg/kg, q24h, PO
Enrofloxacin	Baytril	5-20 mg/kg, q12-24h, PO, IM, SC, IV	5 mg/kg, q24h, PO, IM, SC, IV
Marbofloxacin Orbafloxacin	Zeniquin Orbax	2.75-5.5 mg/kg, q24h, PO 2.5-7.5 mg/kg, q24h, PO	2.75-5.5 mg/kg, q24h, PO 2.5-7.5 mg/kg, q24h, PO
Potentiated sulfas			
Ormetoprim-sulfadimethoxine	Primor	55 mg/kg, q24h day 1, then 27.5 mg/kg, q24h, PO	
Trimethoprim-sulfonamide	Tribrissen (sulfadiazine)	15-30 mg/kg, q12h, PO	15-30 mg/kg, q12h, PO
Tetracyclines			
Doxycycline§ Minocycline Tetracycline	Minocin	5-10 mg/kg, q12-24h, PO, IV 5-12.5 mg/kg, q12h, PO, IV 22 mg/kg, q8-12h, PO	5-10 mg/kg, q12-24h, PO, IV 5-12.5 mg/kg, q12h, PO, IV 22 mg/kg, q8-12h, PO
Antiviral			
Alpha interferon (routine infections)	Intron A		30 IU, q24h, PO
Alpha interferon (life-threatening viral infection)	Intron A	10,000-20,000 IU/kg, SC	10,000-20,000 IU/kg, SC
AZT	Retrovir		5-10 mg/kg, q8-12h, PO
Antiprotozoai			
Babesia spp. Atovaquone Clindamycin hydrochloride Imidocarb diproprionate Metronidazole Cryptosporidium spp.	Antirobe Imizol Flagyl	13.3 mg/kg, q8h, PO 12.5 mg/kg, q12h, PO 5-6.6 mg/kg, q14d, SC or IM 25 mg/kg, q8-12h, PO	
Azithromycin Tylosin	Zithromax	10 mg/kg, q12-24h, PO	10 mg/kg, q12-24h, PO
Cytauxzoon felis Azithromycin			10 mg/kg, q24h, PO

Drugs Used to Treat Infectious Diseases of Dogs and Cats and General Dosing Guidelines\*—cont'd

DRUG	TRADE NAME	CANINE DOSAGE	FELINE DOSAGE
Diminazene			2 mg/kg, q7d, IM
Imidocarb			2 mg/kg, q14d, IM
Parvaquone			10-30 mg/kg, q24h, IM or SC
Buparvaquone			10 mg/kg, q24h, IM or SC
Giardia spp.			10 mg/kg, q24n, lwt or 30
Febantel/pyrantel/praziquantel	Drontal Plus	John Jose PO deily V 2 days	50 mg/kg (fobastol) g24b PO
	Dionial Flus	Label dose, PO, daily × 3 days	50 mg/kg (febantel), q24h, PO × 5 days
Fenbendazole		$50 \text{ mg/kg, PO, q24h} \times 3-5 \text{ days}$	$50 \text{ mg/kg}$ , PO, q24h $\times$ 3-5 days
Metronidazole		15-25 mg/kg, PO, q24h $ imes$ 7 days	25 mg/kg, PO, q24h $\times$ 7 days
Hepatozoon canis			
Trimethoprim-sulfadiazine		15 mg/kg, q12h, PO	
Pyrimethamine		0.25 mg/kg, q24h, PO	
Clindamycin	Antirobe	10 mg/kg, q8h, PO	
Decoquinate	Deccox	10 to 20 mg/kg, q12h, PO	
Imidocarb dipropionate Neospora caninum		5-6 mg/kg, q14d, IM or SQ	
Trimethoprim-sulfadiazine		15 mg/kg, q12h, PO	
Pyrimethamine		1 mg/kg, q24h, PO	
Ćlindamycin		10 mg/kg, q8h, PO	
Toxoplasma gondii		37 (37 4-17)	
Azithromycin		10 mg/kg, q12-24h, PO	10 mg/kg, q12-24h, PO
Clindamycin		12.5 mg/kg, q12h, PO	12.5 mg/kg, q12h, PO
Trimethoprim-sulfadiazine		15 mg/kg, q12h, PO	15 mg/kg, q12h, PO
Antifungal			
Amphotericin B (regular)		0.25 mg/kg, IV as test dose, then 0.5 mg/kg, IV, up to 3	0.25 mg/kg, IV, up to 3 times weekly
		times weekly	
Amphotericin B (regular)		0.5-0.8 mg/kg, SQ, 2-3 times weekly	0.5-0.8 mg/kg, SQ, 2-3 times weekly
Amphotericin B (liposomal)	Abelcet	0.5 mg/kg, IV as test dose, then 1.0 mg/kg, IV, 3-5 times weekly	0.5 mg/kg, IV as test dose, then 1.0 mg/kg, IV, 3-5 times weekly
Fluconazole	Diflucan	5.0 mg/kg, q12-24h, PO	50 mg/cat, q12-24h, PO
Flucytosine¶	Ancobon	50 mg/kg, q8h, PO	50 mg/kg, q8h, PO
Itraconazole	Sporonox	5 mg/kg, q12h, PO for 4 days, then 5-10 mg/kg, q24h, PO	50-100 mg/cat, PO, daily
Ketoconazole	Nizofal	10 mg/kg, q24h, PO	10 mg/kg, q24h, PO
Anti-rickettsial		0. 0. 1	J. J. 1
Ehrlichia spp.			
Doxycycline		10 mg/kg, q24h, PO	10 mg/kg, q24h, PO
Chloramphenical		25-50 mg/kg, q8h, PO, SC, IV,	J. J. 1
lmidocarb		5.0-6.6 mg/kg, q14d, IM, SC	5.0 mg/kg, q14d, IM, SC
Rickettsia rickettsii		=	יייי ושי ישר קשר לשרי לשרי
Doxycycline		10 mg/kg, q24h, PO	
Chloramphenicol		25-50 mg/kg, q8h, PO, SC, IV,	
Enrofloxacin		5 mg/kg, q24h, PO, SC, IM, IV	

IM, Intramuscular; IV, intravenous; SC, subcutaneous; PO, oral.
\*The dose ranges and intervals in this table are general. Please see appropriate sections to determine the optimal dose and duration of therapy for specific syndromes or infections.

<sup>†</sup>For simple infections, azithromycin can be given daily for 3 days and then every third day.

‡The maximum daily dose should be 50 mg/kg.

§The drug can be given once daily to cats for the treatment of simple infections and to dogs and cats with ehrlichiosis.

||Clindamycin, pyrimethamine, and trimethoprim-sulfadiazine are generally used together for acute disease, and decoquinate is used for longterm maintenance therapy.

<sup>¶</sup>This drug is generally used in combination with other antifungal drugs.

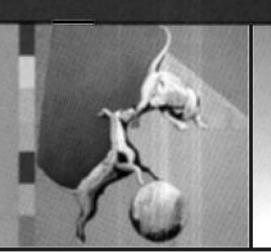
# PART FOURTEEN

# IMMUNE-MEDIATED DISORDERS

J. CATHARINE SCOTT-MONCRIEFF

CHAPTE

# Pathogenesis of Immune-Mediated Disorders



# CHAPTER OUTLINE

GENERAL CONSIDERATIONS AND DEFINITION IMMUNOPATHOLOGIC MECHANISMS PATHOGENESIS OF AUTOIMMUNE DISORDERS PRIMARY VERSUS SECONDARY IMMUNE-MEDIATED DISORDERS

Organ systems involved in autoimmune disorders

# GENERAL CONSIDERATIONS AND DEFINITION

Immune-mediated disorders occur when the protective immune response is activated inappropriately, resulting in organ injury. Pathologic immune responses may occur in response to infectious pathogens and contribute to the clinical disease presentation for that pathogen (e.g., the hemolytic anemia associated with Mycoplasma hemofelis infection) or be stimulated by otherwise innocuous foreign substances (e.g., the allergic reactions that occur to house dust) or by self-antigens (primary autoimmunity). Autoimmunity is defined as a condition characterized by a specific humoral or cell-mediated immune response against constituents of the body's own tissues (self-antigens or autoantigens). The term primary autoimmune disease is reserved for disorders in which no underlying cause can be identified and the cause of the autoimmunity is believed to be an underlying immune system dysfunction or imbalance. The term secondary autoimmunity (also termed secondary immune-mediated disease) is used to describe immune-mediated disorders in which an underlying reason for the autoimmune response can be identified. Examples of secondary causes of autoimmunity include infection, exposure to certain drugs or toxins, neoplasia, and vaccine administration.

### **IMMUNOPATHOLOGIC MECHANISMS**

Immunopathologic injury occurs by four major mechanisms (Table 101-1). Each mechanism may either be part of an appropriate response to a foreign antigen or an inappropriate response that can lead to allergic or immune-mediated disease. More than one mechanism may be involved in a particular immune-mediated disorder.

Type I hypersensitivity involves the humoral immune system, immunoglobulin E (IgE), and mast cells. Exposure of the immune system to antigens by way of the skin, respiratory tract, or gastrointestinal tract leads to activation of antigen-specific subsets of T-helper lymphocytes and initiation of B-cell differentiation to plasma cells. Plasma cells secrete IgE, which attaches to receptors on mast cells. On future exposure to the same antigen, cross-linking of the IgE molecules on the mast cells occurs, which leads to mast cell degranulation. The potent inflammatory mediators that are released lead to vasodilation, edema, eosinophil chemotaxis, pruritus, and bronchoconstriction. Examples of diseases that are mediated primarily by a type I response include allergic bronchitis (feline asthma) and acute anaphylactic reactions.

Type II (cytotoxic) hypersensitivity involves the binding of antibody (IgG or IgM) to specific molecules on the surface of a cell. This binding typically results in destruction of the cell or receptors on the cell. In unusual situations antibodies may induce a biologic effect, such as stimulation of the thyroid-stimulating hormone receptor and induction of hyperthyroidism in humans with Graves disease. The target of antibody binding may be normal self-antigens, infectious agents bound to the cell surface, or nonbiologic antigens such as drugs bound to the cell surface. Antibodies to selfantigens may come from cell damage, resulting in exposure of previously hidden antigens, similarity between self-antigens and foreign antigens such as infectious agents and drugs, and primary immune system dysfunction or imbalance. Classic examples of diseases mediated by type II mechanisms include autoimmune hemolytic anemia, immune-mediated



TABLE 101-1

Mechanisms of Immunopathologic Injury

TYPE OF MECHANISM	IMMUNE SYSTEM EFFECTORS	ORGAN SYSTEMS COMMONLY AFFECTED	EXAMPLES
Type I (immediate)	Humoral immune system (T-helper cells and B cells), IgE, mast cells, inflammatory mediators	Skin, respiratory tract, gastrointestinal tract	Acute anaphylactic reactions, atopy, allergic bronchitis (feline asthma)
Type II (cytotoxic)	Humoral immune system, IgG and IgM	Hematologic, neuromuscular junction, skin	Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, myasthenia gravis, pemphigus foliaceous
Type III (immune complex)	Soluble immune complexes	Kidney, joints, skin	Glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis
Type IV (delayed type)	Sensitized T lymphocytes, cytokines, neutrophils, and macrophages	Endocrine glands, muscle	Lymphocytic thyroiditis, myositis

thrombocytopenia, pemphigus foliaceous, and myasthenia gravis. Antibodies involved in type II responses are usually tissue specific, and the consequence of antibody binding varies from tissue to tissue. For example, in autoimmune hemolytic anemia antibody binding results in either intravascular or extravascular red blood cell hemolysis, whereas in pemphigus foliaceous antibody binding results in disruption of keratinocyte adhesion and vesicle formation. In myasthenia gravis, antibodies directed against acetylcholine receptors cross-link and internalize the receptors, which results in failure of neuromuscular transmission.

Type III (immune complex) hypersensitivity involves the formation and deposition of soluble immune complexes (predominantly IgG) within tissues. Deposition of immune complexes in tissues results in complement fixation and a localized inflammatory response characterized by mast cell degranulation, platelet activation, and neutrophil chemotaxis. Phagocytosis of immune complexes by macrophages causes release of more inflammatory cytokines. In the presence of antibody excess the inflammatory reaction typically remains localized at the site of the initiating antibody; in the presence of antigen excess, however, soluble immune complexes enter the circulation and become deposited in vascular beds in the kidney, joints, eye, and skin. The location and extent of antibody deposition depend on a number of variables, including complex size, charge, degree of glycosylation, and Ig subclass. Classic examples of diseases mediated by type III mechanisms include infections (e.g., feline infectious peritonitis), glomerulonephritis, systemic lupus erythematosus, and rheumatoid arthritis.

Type IV (delayed-type) hypersensitivity involves the cell-mediated immune system. Exposure to either soluble or cell-associated antigen results in sensitization of specific subsets of T cells. Reexposure to the same antigen results in activation of sensitized lymphocytes, subsequent release of cyto-kines, and recruitment of neutrophils and macrophages.

Cytotoxic destruction of target cells may also occur by this mechanism. Activation of sensitized lymphocytes requires 24 to 72 hours to occur, which is why this type of response is termed "delayed." Persistence of the antigen can result in formation of multinucleate giant cells and tissue granulomas. Examples of diseases mediated by type IV immune responses include the protective immune response to intracellular microbes (e.g., leishmaniasis), contact hypersensitivity, polymyositis, and immune-mediated thyroiditis.

# PATHOGENESIS OF AUTOIMMUNE DISORDERS

In normal animals the adaptive immune system should be tolerant of self. This is achieved by a number of mechanisms that prevent B and T lymphocytes from becoming self-reactive. Most autoreactive B and T cells are deleted during maturation in the thymus, and those that escape to the periphery may undergo peripheral deletion by apoptosis, remain hidden intracellularly, or be rendered anergic in the peripheral circulation. When autoimmunity occurs, these mechanisms responsible for tolerance break down. Factors that may play a role in loss of tolerance include genetics, environmental factors, age, hormonal influences, and other diseases that lead to perturbations of the immune system.

Genetics clearly has an important role in the development of autoimmune disease. In some autoimmune diseases certain breeds of dog are at increased risk (Table 101-2). Autoimmunity is also reported more commonly in some families than others. The inbreeding that occurs in many dog breeds exacerbates the effects of such familial traits. Familial autoimmunity is not as well documented in the cat, although the Abyssinian and Somali breeds are at increased risk of myasthenia gravis. The underlying genetic changes that result in such predispositions are not yet characterized in the dog and cat.



TABLE 101-2

### Suspected Autoimmune Disorders of Various Organ Systems in Dogs and Cats

		POSTULATED IMMUNOPATHOLOGIC	
ORGAN SYSTEM	DISEASE	MECHANISM	BREED PREDISPOSITION
Hematologic	Immune-mediated hemolytic anemia	Туре II	American Cocker Spaniel, Bichon Frise, Miniature Pinscher, Miniature Schnauzer, Rough- Coated Collie, English Springer Spaniel, Finnish Spitz
	Pure red cell aplasia	Type II	None identified
	Immune-mediated thrombocytopenia	Type II	Cocker Spaniel, Poodle (all varieties), German Shepherd dog, and Old English Sheepdog
	ldiopathic neutropenia	Type II	None identified
Joints	See Table 104-8	Type III	
Skin	Various	Type II, III, and IV	
Eye	Uveitis, retinitis	Type III	
Kidney	Glomerulonephritis	Type III	
Respiratory tract	Allergic rhinitis	Type !	
	Allergic bronchitis (asthma)	Type I	
	Pulmonary infiltrates with eosinophils	Type I	Husky, Malamute
Gastrointestinal tract	Feline stomatitis/gingivitis, lymphocytic plasmacytic enteritis, anal furunculosis (perineal fistula)	Type IV	German Shepherd dog
Neurologic system	Myasthenia gravis	Type II	Abyssinian, Somali
ζ ,	Myositis	Type IV	Boxer, Newfoundland
	Polyradiculoneuritis	Únknown	·
	Granulomatous meningoencephalomyelitis	Unknown	
	Polyarteritis	Unknown	Beagle
Endocrine glands	Thyroiditis (hypothyroidism)	Type IV	Beagle, Golden Retriever
	Adrenalitis (hypoadrenocorticism)		Standard Poodle, Leonberger, Duck Tolling Retriever
	Insulitis (diabetes mellitus)		Keeshond
Multisystemic immune disease	Systemic lupus erythematosus	Type III	German Shepherd dog

Environmental factors are believed to be important in the development of autoimmunity, with exposure to infectious agents either during natural infection or as a result of vaccination being the most common factor identified. Other possible environmental factors include environmental toxins and drug exposure. Some drugs have been clearly linked to induction of autoimmunity, and many other drugs can likely cause idiosyncratic autoimmune reactions. Examples include the risk of systemic immune disease (polyarthritis, glomerulonephritis, cutaneous lesions, retinitis, polymyositis, anemia, thrombocytopenia) in Doberman Pinschers treated with trimethoprim-sulfadiazine and development of immunemediated hemolytic anemia in some cats treated with thioureylene drugs such as propylthiouracil and methimazole. Myasthenia gravis has also been reported in cats treated with methimazole.

Mechanisms by which infectious agents may induce autoimmunity include molecular mimicry, exposure of cryptic antigens after cellular damage, nonspecific polyclonal activation by superantigens, production of interferon-γ that induces major histocompatibility complex class II expression on cells that do not usually express them (e.g., thyroid follicular cells), and the innocent bystander effect in which the immune response is directed against a microbial antigen or other antigens on the surface of the cell. A complicating factor is that some infections (e.g., ehrlichiosis, borreliosis, and many other vector-borne diseases) may either mimic an autoimmune disease or cause true autoimmunity, and clinically differentiating which of the two is happening can be difficult. This is clinically relevant because the clinician is faced with a decision whether to include immunosuppressive drugs in the treatment protocol.

The role of vaccination in the precipitation of autoimmunity is unclear. Currently most of the evidence is based on anecdotal observation of a temporal association of immune-mediated disease with vaccination. A cause-and-

effect relation has been difficult to establish definitively because of the high prevalence of vaccination and the low incidence of reported adverse effects. Specific evidence for association of individual disease syndromes with vaccination is discussed in the sections on individual diseases. Altered immunoregulation and evidence of immune-mediated disease may also occur in other underlying diseases such as lymphoid neoplasia, IgA deficiency, and after chemotherapy administration.

# PRIMARY VERSUS SECONDARY IMMUNE-MEDIATED DISORDERS

Infection, drug therapy, neoplasia, and possibly vaccination may cause secondary autoimmunity. Investigation for the presence of these factors in dogs and cats with immunemediated disease is important because the presence of underlying disease may influence the treatment and the prognosis. Clearly the presence of a serious underlying disorder such as neoplasia influences the prognosis negatively. Theoretically the presence of a treatable underlying disorder should make controlling the autoimmune process easier. Unfortunately, documentation of a better prognosis with immune-mediated disorders that have an identifiable and treatable underlying disease is lacking in the dog and cat. The presence of concurrent disease may also influence choice of treatment. In particular more potent immunosuppressive drugs may be initially withheld in the presence of an underlying infectious ctiology.

# ORGAN SYSTEMS INVOLVED IN AUTOIMMUNE DISORDERS

Any organ system in the body may be damaged by immune-mediated disease processes (see Table 101-2). The

most common systems involved in the dog and cat are the joints, skin, kidney, and hematologic system, although in general immune-mediated diseases are less common in the cat than the dog. Other organs commonly involved in immune-mediated diseases are the eye, neurologic system, gastrointestinal tract, respiratory tract, and endocrine glands (see Table 101-2). Some immune-mediated diseases such as systemic lupus erythematosus involve multiple organ systems, although not all organ systems may be involved in every animal. Dogs with systemic immune-mediated disorders not uncommonly present with one manifestation of the disorder (e.g., immune-mediated hemolytic anemia) and later relapse with another (e.g., idiopathic thrombocytopenia purpura, polyarthritis). In some of these cases the underlying disorder may be systemic lupus erythematosus, but this is not always the case. A large number of autoimmune diseases affect the dog and cat. The autoimmune disorders discussed in detail in the sections that follow focus on the more-common autoimmune diseases, especially those in which the treatment of choice is immunosuppression. Other disorders in which the pathogenesis is immune mediated, but in which immunosuppression is not part of the treatment (e.g., hypothyroidism from thyroiditis), are discussed in the sections on diseases of the appropriate organ system.

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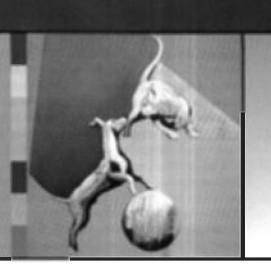
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# CHAPTER

# Diagnostic Testing for Autoimmune Disease



# CHAPTER OUTLINE

### CLINICAL DIAGNOSTIC APPROACH SPECIFIC DIAGNOSTIC TESTS

Coombs Test (Direct Antiglobulin Test)
Slide Agglutination Test
Antiplatelet Antibodies
Megakaryocyte Direct Immunofluorescence
Antinuclear Antibody Test
Lupus Erythematosus Test
Rheumatoid Factor
Immunofluorescence and Immunohistochemistry
Autoimmune Panels

### CLINICAL DIAGNOSTIC APPROACH

The diagnostic approach to a dog or cat with suspected immune-mediated disease depends on the clinical presentation and organ(s) involved. A complete history including questions regarding environmental or drug exposures, previous medical history, exposure to infectious agents, and vaccination history should be obtained. A thorough physical examination should also be performed. The next step is to define the extent of the problem and rule out other more common causes of the clinical signs. A typical minimal database includes a complete blood count, serum biochemical profile, and urinalysis. Because many immune-mediated diseases are characterized by fever and leukocytosis, ruling out infectious agents as the primary cause of the clinical signs is important before pursuing other less common causes. The diagnostic evaluation for immune-mediated disease is similar to that for fever of unknown origin. Bacterial culture of the urine, blood, or both—testing for common viral pathogens such as feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis-and diagnostic imaging (thoracic and abdominal radiographs, abdominal ultrasound) are important. Investigation for vector-borne diseases such as ehrlichiosis, anaplasmosis, borreliosis, and

leishmaniasis as well as more fastidious organisms such as mycoplasma and L-forms, is usually only considered once more common bacterial and viral infections have been excluded because these tests are more expensive and the results are often not immediately available. The specific infectious agents tested for depend on whether the patient is a dog or cat as well as the disease presentation and geographic location because many infectious diseases have regional distributions.

If infection is ruled out or considered unlikely, further diagnostic evaluation should focus on organs identified as potentially involved according to the physical examination and results of the minimal database and diagnostic imaging. Organ-specific diagnostic tests may include evaluation of joint or cerebrospinal fluid, quantification of urine protein excretion, and biopsy of affected organs. (These tests are discussed in more detail in the sections on specific diseases.)

Specific tests of immune dysfunction are indicated once infectious and neoplastic diseases have been excluded and when the organ system(s) of interest has been identified. For example, in a dog with a regenerative anemia the clinician should consider doing a direct antiglobulin (Coombs) test, whereas in a dog with polyarthritis a test for rheumatoid factor would be indicated. Immune panels that include a selection of tests with different indications are rarely necessary and may result in excessive testing and results that are difficult to interpret. For example, a positive Coombs test has little relevance in a dog that is not anemic.

#### SPECIFIC DIAGNOSTIC TESTS

# COOMBS TEST (DIRECT ANTIGLOBULIN TEST)

The direct Coombs test, or direct antiglobulin test (DAT), detects the presence of antibody and/or complement bound to patient red blood cell (RBC) membranes. The test is used for diagnosis of immune-mediated hemolytic anemia (IMHA) and for diagnosis of hemolytic transfusion reactions. The DAT uses antidog or anticat antiglobulin antibody produced in a different species (usually goats or rabbits); the

reagents are species specific. The DAT is best performed on ethylenediamine tetraacetic acid (EDTA) anticoagulated blood at body temperature (37° C). Most frequently a combined Coombs reagent containing goat anticanine immunoglobulin (Ig) G, IgM, and complement component C3 is used. Addition of the Coombs reagent to washed patient RBCs results in agglutination if more than approximately 100 IgG antibody or C3 molecules are bound to the RBCs. Because the end point of the test is agglutination, the test cannot be interpreted if spontaneous agglutination persists after washing the RBCs. Results of the DAT may be reported in various forms depending on the laboratory: positive or negative, 1+ to 4+ agglutination, or as the lowest dilution of the reagent that results in agglutination. Modifications of the DAT that may improve diagnostic performance include use of monospecific antisera (usually IgG, IgM, and C3), and using more dilutions of the reagents than typically performed. The pattern of the antibody binding (IgG vs. IgM, vs. C3) can be used to increase specificity of the DAT because some patterns of binding tend to be more specific for IMHA than others. For example, in dogs with IMHA the most common pattern of binding is IgG and C3, whereas C3 alone is most commonly seen in dogs with nonhemolytic disorders and underlying inflammatory or neoplastic diseases. Using more dilutions of reagent can potentially improve the sensitivity of the DAT because it allows detection of the prozone effect in which a lack of reactivity is observed with high concentrations of antibody. Another modification of the DAT involves performing the test at 4° C to identify coldacting agglutinins. This test should only be used in animals with clinical signs of cold agglutinin disease (e.g., ear or tail tip necrosis) because nonspecific RBC agglutination occurs commonly at 4° C in many normal dogs. In some dogs with IMHA that have spontaneous agglutination, agglutination will resolve after washing of the RBCs. In this scenario a DAT may still be indicated because resolution of a previously positive DAT may be useful for disease monitoring. Both false-positive and false-negative results may occur with the DAT (Box 102-1). For this reason the DAT should be interpreted in the light of other clinical and clinicopathologic information. Recognizing that a positive Coombs test does not distinguish primary from secondary IMHA is also

important (see Chapter 104). Other more sensitive techniques such as enzyme-linked antiglobulin tests, flow cytometric techniques, and column agglutination assays have also be used to detect the presence of antibody on RBCs; however, these tests are not yet widely available in commercial laboratories.

The indirect antiglobulin test is used to detect antibody in patient serum that is capable of binding to RBCs collected from a different animal. This test is both less sensitive and less specific than the direct test and is rarely used clinically except when screening blood donor serum for anti–dog erythrocyte antigen antibodies or as part of some crossmatching procedures.

#### **SLIDE AGGLUTINATION TEST**

The slide agglutination test is used to detect the presence of spontaneous agglutination of RBCs. Spontaneous agglutination (autoagglutination) is a three-dimensional clustering of RBCs that occurs from cross-linking of RBC surface-associated antibodies. Autoagglutination occurs as a result of the presence of either high titer IgG or IgM on the RBC membrane. Agglutination must be distinguished from rouleaux formation (stacking of RBCs that occurs most often in the presence of high globulin concentrations). To evaluate for the presence of agglutination, 1 drop of saline should be added to 5 to 10 drops of blood and mixed. The RBC suspension is then evaluated both by macroscopic and microscopic examination at a temperature as close to 37° C as possible. The temperature is important because clinically insignificant cold-acting agglutinins are common in normal dogs. In most laboratories spontaneous autoagglutination that persists after saline dilution is considered diagnostic for IMHA. In other laboratories only RBC agglutination that persists after three washings of the RBCs is considered diagnostic for IMHA.

# ANTIPLATELET ANTIBODIES

Detection of platelet surface—associated antibody (direct antibody) or serum platelet bindable antibody (indirect antibody) may be useful in evaluation of dogs and cats with



BOX 102-1

Causes of False-Positive and False-Negative Results for the Direct Antiglobulin (Coombs Test)

### **FALSE-POSITIVE RESULT**

Chronic inflammatory disease

Technical problems (contamination, overcentrifugation)

Poor sample quality (clotted samples, use of serum separator tubes, collection from dextrose containing infusion lines)
Septic patient

Clinically insignificant, naturally occurring cold autoantibody Hypergammaglobulinemia

Interference by drugs (e.g., amiodarone)

### **FALSE-NEGATIVE RESULT**

Technical problems (washing, dilution, centrifugation errors)
Delay in running test (e.g., mail-in samples)
Contamination or repeated freezing of reagents
Low quantities of antibody present on cell

suspected immune-mediated thrombocytopenia. Tests for antiplatelet antibody are most commonly performed by using flow cytometric techniques. Detection of platelet surface-associated IgG is more sensitive than detection of serum platelet-bindable antibodies, presumably because the majority of antiplatelet antibody is bound to platelets rather than free in the circulation. The direct assay has a sensitivity of greater than 90% in dogs with confirmed idiopathic thrombocytopenic purpura (ITP). Because of the high sensitivity of the direct assay, a negative result for platelet surface-associated antibody makes a diagnosis of ITP unlikely. Detection of antiplatelet antibodies by either the direct or indirect technique implies an immune-mediated pathogenesis for thrombocytopenia but is not specific for primary immune-mediated thrombocytopenia. Many infectious and neoplastic diseases as well as drug exposure may cause thrombocytopenia by immune-mediated mechanisms; therefore blood samples from such patients may be positive for platelet-associated antibody. A flow cytometric assay for platelet surface-associated antibody for both dogs and cats is currently available at Kansas State University. The test requires 2 mL of EDTA blood and currently costs \$60 plus shipping. Blood samples should be shipped overnight on ice.

### **MEGAKARYOCYTE DIRECT IMMUNOFLUORESCENCE**

Antibodies directed against megakaryocytic cells in the bone marrow may be detected by direct immunofluorescence (see below for more details on immunofluorescent testing). Variable sensitivity (30% to 80%) for diagnosis of ITP has been reported. This test is also offered at Kansas State University and costs \$40. A bone marrow aspirate is required, and slides should be air dried before being sent to the testing laboratory.

### **ANTINUCLEAR ANTIBODY TEST**

Measurement of antinuclear antibody (ANA) is useful in the evaluation of dogs and cats with suspected systemic lupus erythematosus (SLE). SLE should be suspected in patients with evidence of an immune-mediated process affecting a minimum of two organ systems (see Chapter 104). Antinuclear antibodies are heterogenous antibodies directed against nuclear antigens. They are typically detected by immunofluorescent staining of frozen sections of rat liver or tissue culture monolayers of human epithelial cell lines. Results are reported as a titer that is the highest dilution of patient serum that causes definitive immunofluorescent nuclear staining. Various patterns of nuclear staining (diffuse, speckled, peripheral, and nucleolar) can be identified, but the clinical significance of the various staining patterns is still under investigation in dogs and cats. Measurement of ANA antibodies is sensitive for diagnosis of SLE in dogs and cats, although ANA-negative cases of SLE do occur. In one study of 75 dogs with SLE, 100% had a positive ANA titer (Fournel et al., 1992). In most cases the ANA titer was greater than 1:256 and the magnitude of the titer correlated with disease severity. Other studies have demonstrated lower sensitivity

of the ANA for diagnosing SLE. The variability in diagnostic sensitivity probably arises from differences in stringency in the diagnostic criteria for confirming a diagnosis of SLE and variability among laboratories in assay sensitivity and specificity. Many normal animals have low positive titers for ANA, so a cut-off for a significant positive titer should be established for each individual laboratory. The cut-off titer varies depending on the substrate and techniques used by the laboratory. Low positive ANA titers may also occur after exposure to certain drugs and in animals with chronic inflammatory or neoplastic diseases. ANAs are detected in 10% to 20% of dogs with seroreactivity to Bartonella vinsonii, Ehrlichia canis, and Leishmaniasis infantum. Dogs with seroreactivity to multiple pathogens are more likely to be ANA positive. Chronic or high-dose corticosteroid treatment may decrease the ANA titer.

#### LUPUS ERYTHEMATOSUS TEST

The lupus erythematosus (LE) test is a highly specific test for SLE but is rarely used clinically because it lacks sensitivity and the ANA test is more sensitive and less time consuming. LE cells are neutrophils that contain phagocytosed nuclear material. The test is performed in vitro. Blood collected from the patient is allowed to clot and is damaged to release free nuclei. If ANA is present it binds to nuclear material and the resulting complex is phagocytosed by neutrophils and can be identified as an LE cell by visual inspection. LE cells may also rarely be identified in vivo in blood, bone marrow, or joint fluid and, when present, are highly suggestive of SLE. The LE cell test is more sensitive to the effects of steroids than is the ANA titer. The test has been reported to be positive in the blood of 30% to 90% of dogs with SLE but may also be positive in other immune or neoplastic disorders.

#### RHEUMATOID FACTOR

Rheumatoid factor (RF) is antibody directed against an individual's own IgG. The antibody is directed against sites on the Fc portion of immunoglobulin molecules that become exposed only after antibody binds to antigen. The test is used as one of the diagnostic criteria for rheumatoid arthritis; however, the utility of the test is limited by a lack of sensitivity and specificity. The most common technique for detection of RF is the Rose-Waaler, test which uses sheep RBCs sensitized to rabbit IgG. If RF is present in patient serum, agglutination occurs. The test is performed on refrigerated serum. Samples should not be frozen because RF activity may be destroyed. Only 40% to 75% of dogs with rheumatoid arthritis are positive for RF, so a negative titer does not rule out the disease. In addition, any disease with longstanding immune complex formation may eventually cause RF, so a positive titer should not be the sole criterion for a diagnosis of rheumatoid arthritis.

### **IMMUNOFLUORESCENCE AND IMMUNOHISTOCHEMISTRY**

In many type II and type III immune-mediated diseases the presence of antibody in fixed tissues (e.g., kidney, skin) can TABLE 102-1

Clinical Indications for Use of Diagnostic Tests in Suspected Autoimmune Disease

CLINICAL SYNDROME	POTENTIAL IMMUNE- MEDIATED CONDITIONS TO CONSIDER	TESTS INDICATED TO CONFIRM	LIMITATIONS
Anemia (regenerative or nonregenerative)	Immune-mediated hemolytic anemia, pure red cell aplasia	Coombs test, slide agglutination test, review of CBC smear for spherocytes or ghost cells Bone marrow aspirate and core (if anemia is nonregenerative)	A negative Coombs test result does not rule out immune- mediated hemolytic anemia; false-positive Coombs test results may also occur
Thrombocytopenia	Immune-mediated thrombocytopenia, infectious causes of thrombocytopenia, megakaryocytic aplasia	Platelet-associated antibody, platelet-bindable antibody, bone marrow aspirate and core	Positive platelet-associated antibody test does not distinguish primary from secondary immune-mediated hemolytic anemia
Anemia and thrombocytopenia	IMHA, Evans syndrome	Coombs test Slide agglutination test Review of slide for spherocytes or ghost cells Platelet-associated antibody, platelet-bindable antibody, bone marrow aspirate and core	May be hard to distinguish blood loss anemia from hemolytic anemia in dogs with severe thrombocytopenia; Coombs test may be positive after transfusion
Shifting leg lameness, joint pain, or effusion	Nonerosive polyarthritis SLE, rheumatoid arthritis	Synovial fluid collection, radiographs of joints, RF, ANA (if other organ systems involved)	Negative RF does not rule out rheumatoid arthritis; in early rheumatoid arthritis erosive changes may not be present
Proteinuria	Glomerulonephritis	Urinalysis; protein/creatinine ratio; renal biopsy for histopathology, immunofluorescence, electron microscopy	Need to rule out inflammation arising from the lower urinary tract prior to interpreting protein/creatinine ratio
Two of the above clinical syndromes together or in combination with dysfunction of other organ system	SLE	ANA, LE preparation	LE has very low sensitivity for diagnosis of SLE; ANA titer is more sensitive, but some dogs with SLE may have a negative ANA

ANA, antinuclear antibody; IMHA, immune-mediated hemolytic anemia; LE, lupus erythematosus; SLE, Systemic lupus erythematosis.

be detected by immunofluorescent or immunoperoxidase techniques. Numerous variations on these methods exist, but in general, sections of tissue are labeled with a primary antibody (e.g., rabbit antidog IgG) and then a secondary antibody is added (e.g., antirabbit IgG), which has been conjugated to either fluorescein or the enzyme peroxidase. If antibodies are present in the tissue sample, apple green fluorescence is seen under ultraviolet light with immunofluorescent staining. In the case of immunoperoxidase peroxide, when a substrate is added in the presence of hydrogen peroxide, deposition of a brown color can be visualized with the light microscope. Tissue samples for immunofluorescent testing should be collected in Michel's medium. Routinely fixed tissue can be used for immunohistochemistry.

Common uses for immunofluorescent staining include evaluation of renal biopsies in dogs with suspected glomer-ulonephritis, detection of antibodies directed against mega-karyocytic cells in the bone marrow, and evaluation of skin biopsies from patients with suspected autoimmune skin disease.

# **AUTOIMMUNE PANELS**

Many laboratories offer an immune panel that typically includes a complete blood count and platelet count, Coombs test, ANA, and RF. It would be unusual for all these tests to be appropriate in an individual patient (Table 102-1). In addition to the cost of running such a panel, the significance of a positive test may be difficult to determine in patients in

which the test was initially not indicated. For these reasons the clinician is encourage to pick individual tests rather than automatically choosing an autoimmune panel in a dog or cat with suspected autoimmune or immune-mediated disease.

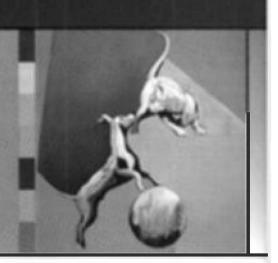
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# CHAPTER

# Treatment of Primary Immune-Mediated Diseases



# CHAPTER OUTLINE

PRINCIPLES OF TREATMENT OF IMMUNE-MEDIATED DISEASES
OVERVIEW OF IMMUNOSUPPRESSIVE THERAPY
GLUCOCORTICOIDS
AZATHIOPRINE
CYCLOPHOSPHAMIDE
CHLORAMBUCIL
CYCLOSPORINE
VINCRISTINE
DANAZOL
HUMAN INTRAVENOUS IMMUNOGLOBULIN
PENTOXIFYLLINE
SPLENECTOMY

# PRINCIPLES OF TREATMENT OF IMMUNE-MEDIATED DISEASES

When treating an animal with immune-mediated disease, any underlying disease must also be treated. Although concurrent immunosuppressive therapy is typically necessary, effective treatment of underlying disease (if possible) may minimize the length of immunosuppressive therapy. The aim of treatment is to control the immune-mediated process while minimizing the adverse effects of the drugs used. In many situations short-term adverse effects must be tolerated to put the immune-mediated disease into remission. In the long term, however, medications must be tapered to minimize adverse effects. If this is not possible or if the initial drug chosen elicits a poor response, alternate or additional therapy should be considered. Monitoring the disease process before each dose reduction is critical and should be individualized depending on the underlying disease process. For example, in immune-mediated hemolytic anemia (IMHA), monitoring the complete blood count (CBC) and reticulocyte count (plus the Coombs test if it was initially positive) is adequate, whereas in dogs with immune-mediated polyarthritis repeated joint taps for synovial fluid analysis are recommended.

Supportive care and aggressive monitoring for complications caused by the immunosuppressive drugs is also critical. Detection and treatment of complications of therapy can improve long-term outcome and minimize adverse sequelae. For example, patients receiving glucocorticoids should be carefully monitored for evidence of gastrointestinal ulceration, and animals receiving azathioprine should be monitored for hepatotoxicity and bone marrow suppression. In addition, supportive care is also needed while waiting for the full effects of immunosuppressive therapy. For example, dogs with IMHA and immune-mediated thrombocytopenia (ITP) may require several transfusions before immunosuppressive treatment adequately controls the immunemediated destruction of red blood cells (RBCs) or platelets. Other forms of supportive care that may be necessary include care of the skin in animals that are recumbent, nutritional support, monitoring for and treatment of infection, and prevention of gastrointestinal ulceration.

# OVERVIEW OF IMMUNOSUPPRESSIVE THERAPY

The first line of treatment for the majority of immunemediated diseases is treatment with glucocorticoids (Table 103-1). The reasons for using glucocorticoids as the first line of therapy include rapid onset of action, low risk of toxicity, and low cost. Even in patients with concurrent conditions such as diabetes mellitis, in which long-term glucocorticoid treatment is relatively contraindicated, glucocorticoids should still be used initially with a plan to transition to other drugs (such as azathioprine) that are less likely to complicate management of the concurrent disease. In some immunemediated diseases additional immunosuppressive drugs should be added at the start of treatment. These are diseases in which a positive response to glucocorticoids alone is unlikely. Examples include canine Evans syndrome, canine IMHA with multiple poor prognostic indicators (intravascular hemolysis, agglutination that persists after washing the

RBCs, high bilirubin concentration), systemic lupus erythematosus, rheumatoid arthritis, and the polyarthritis syndrome of Akitas. In most other immune-mediated diseases, the response to glucocorticoids should be assessed before adding other immunosuppressive drugs. If response to glucocorticoids is inadequate or the adverse effects of glucocorticoids are unacceptable, azathioprine is the next drug that is most commonly added to the treatment protocol in the dog, and chlorambucil should be considered in the cat. Cyclophosphamide and cyclosporine are typically considered third-line drugs, although some exceptions are discussed in the sections on the individual immune-mediated diseases (see Chapter 104). For example, cyclosporine is used as a first-line drug in treatment of perianal fistulas in dogs, and cyclophosphamide is used as a second-line drug in cats with red cell aplasia. If immune-mediated disease has an underlying infectious cause, more caution should be used before adding an additional immunosuppressive drug. When adding a third-line drug, in most circumstances it should replace the second-line drug. Treatment with more than one additional immunosuppressive drug at the same time (e.g., azathioprine and cyclosporine together) is usually unneces-



# TABLE 103-1

First-, Second-, and Third-Line Drugs Commonly Used in the Management of Immune-Mediated Disease of the Dog and Cat

	DOG	CAT
Initial treatment Second line Third line	Prednisone Azathioprine Cyclophosphamide or cyclosporine	Prednisolone Chlorambucil Cyclophosphamide or cyclosporine

sary and is likely to cause much more severe immunosuppression and predisposition to infection.

# **GLUCOCORTICOIDS**

Glucocorticoids (corticosteroids with primarily glucocorticoid activity) are the mainstay of treatment of most immunemediated diseases because they are effective, rapid acting, and cheap. Several different glucocorticoid drugs vary according to duration, potency, and route of administration. Glucocorticoids are characterized by their biologic half-life as measured by duration of suppression of the hypothalamic pituitary adrenocortical axis (Table 103-2). Short-acting glucocorticoids such as hydrocortisone and cortisone have a biologic half-life of less than 12 hours. Intermediate-acting steroids such as prednisone, prednisolone, methylprednisolone, and triamcinolone have a biologic half-life of 12 to 36 hours, and betamethasone, dexamethasone, flumethasone, and paramethasone have a biologic half-life of 48 hours or longer. The duration of effect of a glucocorticoid preparation is also influenced by the chemical form of the steroid. Parenteral glucocorticoid preparations are either esters or free steroid alcohols. Highly soluble esters (e.g., dexamethasone sodium phosphate, prednisolone sodium succinate) and solutions of free steroid alcohols in polyethylene glycol (dexamethasone, flumethasone) have a duration of action similar to the biologic half-life, but long-acting suspensions of insoluble steroid esters (e.g., methylprednisolone acetate suspension, triamcinolone acetamide suspension) are absorbed slowly from the injection site and do not achieve high plasma concentrations. The slow absorption also dramatically prolongs the duration of effect. Oral preparations are usually composed of the free steroid alcohol; because absorption from the gastrointestinal tract is quite rapid, the duration of effect is similar to the biologic half-life. The



Comparison of the Properties of Synthetic Glucocorticoids

COMPOUND	DURATION OF ACTION*	ANTIINFLAMMATORY POTENCY	EQUIVALENT DOSE (mg)	MINERALOCORTICOID POTENCY	APPROPRIATE FOR ALTERNATE DAY USE
Cortisone	Short	0.8	5.0	0.8	No
Hydrocortisone	Short	1.0	4.0	1.0	No
Prednisone/ prednisolone	Intermediate	4.0	1.0	0.3	Yes
Methylprednisolone	Intermediate	5.0	0.8	0	Yes
Triamcinolone	Intermediate (up to 48 hr)	5.0	0.8	0	No
Paramethasone	Long	10.0	0.4	0	No
Flumethasone	Long	15.0	0.3	0	No
Dexamethasone	Long	30.0	0.15	0	No
Betamethasone	Long	35.0	0.12	0	No

Reprinted from Behrend EN et al: Pharmacology, indications, and complications, Vet Clin North Am Small Anim Pract 27:187, 1997. 
\*Short = <12 hours; intermediate = 12 to 36 hours; long = >48 hours.

antiinflammatory effects of corticosteroids correlate with their glucocorticoid activity, and undesirable adverse effects such as sodium retention and edema formation are associated with mineralocorticoid activity. Synthetic steroids that possess higher glucocorticoid and lower mineralocorticoid activity than cortisol include prednisone, which has four times the potency of cortisone but 0.3 times the mineralocorticoid activity; dexamethasone, which has eight times the potency with no mineralocorticoid activity; and triamcinolone, which also has no mineralocorticoid activity.

In most patients with immune-mediated disease the ideal route of glucocorticoid administration is oral; however, in animals that are vomiting or have diseases that interfere with swallowing or gastrointestinal absorption, intravenous administration of either prednisolone or dexamethasone may be necessary. The use of long-acting parenteral drugs for treatment of immune-mediated disease is not recommended because of the failure to achieve high plasma concentrations and the long duration of effect.

The actions of corticosteroids that make them useful drugs in the treatment of various immune-mediated diseases are shown in Box 103-1. The early effects of corticosteroids are believed to result from a rapid decrease in the phagocytic activity of splenic and hepatic macrophages, whereas the long-term effects result from suppression of cell-mediated immunity. How much suppression of antibody production occurs in steroid-resistant species such as the dog and cat is controversial, but effects on B lymphocytes likely occur from suppression of T-helper cells that are required for full antibody response to an antigen.

For treatment of most immune-mediated diseases, an intermediate-acting corticosteroid such as prednisone is the treatment of choice. Prednisone is converted in the liver to prednisolone. The two drugs have historically been considered clinically identical except in the presence of hepatic failure; however, some evidence now suggests that cats do



#### BOX 103-1

# Actions of Corticosteroids that Play a Role in Treatment of Immune-Mediated Disease

- Inhibition of macrophage and neutrophil phagocytosis and chemotaxis
- Decreased neutrophil margination and migration
- Decreased lymphocyte proliferation
- Decreased numbers of circulating lymphocytes
- Altered cytokine production (decreased production of T-cell cytokines)
- Decreased cellular response to inflammatory mediators
- Inhibition of complement pathways
- Inhibition of immune complex passage through basement membranes
- Decreased prostaglandin and leukotriene synthesis
- Altered expression of phenotypic markers on canine lymphocytes
- Induction lymphocyte apoptosis (in vitro)

not convert prednisone to prednisolone as well as other species, and thus prednisolone may be a better choice than prednisone in cats. The starting dose for prednisone in dogs is 2 to 4 mg/kg/day usually given in two divided doses. Cats are more resistant to the effects of glucocorticoids than are dogs. In cats doses of 2 to 8 mg/kg/day of prednisolone or 4 mg/week per cat of dexamethasone are recommended. For immunosuppressive therapy with other glucocorticoids, the dose is based on the drug's comparative potency to prednisone. For example, the dose of dexamethasone should be approximately eight times less than the dose of prednisone for an equivalent effect. Other than this difference in potency, no evidence currently suggests that dexamethasone is more effective than prednisone or prednisolone in the treatment of immune-mediated disease. The most common reason for choosing dexamethasone rather than prednisone is for parenteral administration in patients that are vomiting or cannot tolerate oral medication.

Although glucocorticoids are extremely useful in the management of immune-mediated disease, long-term adverse effects may be debilitating to the animal and intolerable to the owner. Common adverse effects include polyuria, polydipsia, panting, weakness, dermatologic changes, predisposition to infection, gastrointestinal ulceration (at higher doses) and muscle atrophy (Fig. 103-1). Insulin resistance and hyperglycemia as well as a steroid-induced hepatopathy may also occur. Individual patients vary in their tolerance of the side effects of glucocorticoid therapy, with larger dogs often being particularly sensitive. Cats seem to be much more resistant to the side effects of glucocorticoids than are dogs.

Strategies to minimize the adverse effects of glucocorticoid therapy include using the lowest dose that will control the disease of interest, using shorter acting rather than longer acting steroids, and switching to alternate-day therapy as soon as possible. To maximize the likelihood of a good response to treatment, start with high doses initially and then slowly taper the dose rather than start with a more



FIG 103-1

Severe temporal muscle atrophy in a 7-year-old castrated male Weimaraner treated with immunosuppressive doses of prednisone for immune-mediated disease.

conservative dose and increase the dose if required. Tapering of the dose should be based on an objective measure of response to treatment (e.g., hematocrit or joint fluid analysis), and tapering of the dose should be done slowly to minimize the chance of disease relapse. As a general rule the dose should not be tapered faster than 50% per month. Remission may be harder to achieve a second time if the disease is allowed to relapse because of premature tapering of the dose. If clinical signs of glucocorticoid treatment are intolerable, other immunosuppressive drugs should be added to the treatment protocol so that the dose of glucocorticoids can be tapered more rapidly and ultimately discontinued.

#### AZATHIOPRINE

Azathioprine (Imuran) is a thiopurine antimetabolite that is a sulfur analog of adenine. After absorption, azathioprine is converted into 6-mercaptopurine and then into a number of thiopurine antimetabolites within the liver. The active cytotoxic metabolites of azathioprine are the 6-thioguanine nucleotides, which compete with purines in the synthesis of nucleic acids. This results in formation of nonfunctional nucleic acid strands. DNA and RNA synthesis is inhibited, leading to decreased proliferation of rapidly dividing cells. In hepatic insufficiency the immunosuppressive effects of azathioprine are diminished, and concurrent administration of allopurinol results in increased concentration of active metabolites. Azathioprine has a preferential effect on Tlymphocyte function with inhibition of cell-mediated immunity and T-lymphocyte-dependent antibody synthesis. Numbers of circulating monocytes are also decreased. Some confusion exists in the veterinary literature about the length of time required for azathioprine to have a clinical effect. The experimental data are sparse, but in one study azathioprine inhibited blastogenic response of canine lymphocytes to mitogens after 7 days of treatment, although serum immunoglobulin concentrations were unchanged. Clinical experience, however, suggests that the full effects of azathioprine treatment may not occur until 4 to 8 weeks after initiation of treatment.

Azathioprine is commonly used as a second-line drug in a variety of immune-mediated diseases, including immunemediated hemolytic anemia, immune-mediated thrombocytopenia, immune-mediated polyarthritis, inflammatory bowel disease, and systemic lupus erythematosus (SLE) (see Chapter 104 for the specific indications for each of these diseases). Azathioprine at the typical starting dose of 2 mg/kg PO q24h is well tolerated in dogs. Adverse effects are uncommon but bone marrow suppression, gastrointestinal upset, pancreatitis, and hepatotoxicity have been reported. A small percentage of canine patients experience life-threatening myelosuppression, characterized by neutropenia, thrombocytopenia, and sometimes anemia, when treated with azathioprine. Lower doses of azathioprine (50 mg/m<sup>2</sup> q24h or 1 mg/kg PO q24h) should be considered in dogs that show evidence of myelosuppression at the usual

2 mg/kg dose. Attempts to predict which patients are likely to have these reactions by measuring thiopurine methyltransferase activity have not been rewarding. Bone marrow suppression usually occurs within 1 to 4 months after initiation of therapy and is typically reversible within 7 to 14 days after discontinuation of therapy. Because of the potential for myelosuppression and hepatotoxicity, dogs receiving azathioprine should have a CBC and hepatic enzymes measured every 1 to 2 weeks for the first month of treatment and then every 1 to 3 months. In dogs azathioprine is typically initially used in conjunction with immunosuppressive doses of prednisone. If a positive response is observed to combined therapy, the prednisone dose should be tapered over a period of 2 to 4 months. During this time daily azathioprine should be continued at the same dose (if adverse effects are not seen). If complete discontinuation of prednisone is possible without disease relapse, then the dose of azathioprine can be gradually decreased. This is usually accomplished by initially changing the dose schedule to every other day and then to every third day before complete cessation of treatment. In patients for whom prior relapse of immune-mediated disease has already occurred, the clinician may choose to continue life-long low-dose azathioprine treatment (2 mg/kg every other day). Of note, bone marrow suppression has been reported as long as 12 months after starting azathioprine treatment, so monitoring of CBC and hepatic enzymes should be continued for the duration of treatment. Azathioprine is not recommended for use in cats because severe neutropenia and thrombocytopenia have been reported to occur even at reduced doses. Chlorambucil is a better choice for adjunctive immunosuppression in cats with immune mediated disease.

#### CYCLOPHOSPHAMIDE

Cyclophosphamide (Cytoxan) is an alkylating agent that decreases cell division of both B and T lymphocytes. Alkylating agents form covalent bonds with organic compounds, specifically nucleic acids, with resultant cross-linking of DNA, inhibition of DNA synthesis, and death in rapidly dividing cells. Cyclophosphamide affects both the cell-mediated and the humoral immune responses, but the effects on the humoral system are more pronounced. Cyclophosphamide requires hepatic transformation to its active metabolites (nornitrogen mustard, phosphoramide mustard, and acrolein). Cyclophosphamide is used to treat a range of immune-mediated diseases, but it is less commonly used than azathioprine because of the higher risk of adverse effects. In the past cyclophosphamide was a commonly used drug for adjunctive treatment of dogs with IMHA; however, recent studies suggest that other drugs such as azathioprine and cyclosporine are better choices in this disease. Adverse effects of cyclophosphamide include bone marrow suppression, gastrointestinal upset, poor hair growth, alopecia, and sterile hemorrhagic cystitis from the toxic effects on the bladder of the metabolite acrolein. Sterile hemorrhagic cystitis is most commonly reported in dogs treated with cyclophosphamide for 2 months or longer and is rare in cats. Cyclophosphamide is typically dosed in dogs either at 50 mg/m² daily for 4 days each week or as a single intravenous dose of 200 mg/m² once a week. The latter dose schedule tends to cause more profound bone marrow suppression. Lower doses are recommended in cats (Table 103-3).

# **CHLORAMBUCIL**

Chlorambucil (Leukeran) is an alkylating agent that is most commonly used as an alternative to azathioprine in cats with immune-mediated disease. Chlorambucil is a prodrug metabolized to the active metabolite phenylacetic acid mustard. It can also be used as an alternate immunosuppressive drug in dogs that do not tolerate the more commonly used cytotoxic drugs. The usual starting dose for treatment of immune-mediated diseases in both dogs and cats is 0.1 to 0.2 mg/kg PO q24h or 20 to 40 mg/m² PO q2wk (see Table 103-3). Adverse effects include bone marrow suppression, gastrointestinal upset, and predisposition to infection.

#### **CYCLOSPORINE**

Cyclosporine, a potent immunomodulating agent, is a cyclic polypeptide extracted from fungi. The major mode of action is by inhibition of the initial activation phase of CD4 T lymphocytes. Cyclosporine blocks the transcription of genes encoding several cytokines, in particular interleukin-2 (IL-2). This prevents the activation and proliferation of T lymphocytes and the secondary synthesis of other cytokines. Cyclosporine does not affect the humoral immune system; therefore treatment with cyclosporine should not influence response to vaccination. Cyclosporine is the treatment of choice for perianal fistulas in dogs and is as effective as glucocorticoids in the management of atopic dermatitis. Cyclosporine has also been used to treat other refractory immune-mediated diseases in dogs and cats, such as immune-mediated hemolytic anemia, inflammatory bowel disease, myasthenia gravis, granulomatous meningoencephalomyelitis, pure red cell aplasia, and a variety of immunemediated dermatologic diseases.

Cyclosporine is available as a vegetable oil formulation (Sandimmune, Sandoz, Holzkirchen, Germany) or as a microemulsion in gelatin capsules (Atopica, Novartis Animal Health, Basel, Switzerland; Neoral, Sandoz). Bioavailability of the microemulsion is higher than that of the oil-based product, and drug absorption is less variable. Because food intake delays drug absorption and increases variability of absorption, the microemulsion form of cyclosporine should be given 2 hours before or after feeding. Doses of cyclosporine depend on the product used and the disease being treated but range from 5 mg/kg q24h to 10 mg/kg PO q12h (Tables 103-3 and 103-4). Lower doses are typically necessary when the microemulsion product is used. Measurement

of blood cyclosporine concentration for dose individualization is recommended; however, clear-cut guidelines for appropriate therapeutic concentrations are lacking. In addition, considerable variability exists between commercial assays for cyclosporine, so following the guidelines of individual laboratories regarding the therapeutic range is important. Blood cyclosporine levels measured with high-performance liquid chromatography techniques are typically lower than those measured with other commercial techniques (fluorescent polarization immunoassay, radioimmunoassay) because these techniques also detect some cyclosporine metabolites. Trough concentrations of 400 to 600 ng/mL (depending on the assay used) are considered to be in the therapeutic range, but positive clinical responses for some disorders may be observed at lower concentrations.

Numerous interactions between cyclosporine and other drugs occur because of shared metabolic pathways involving the cytochrome P450 enzyme system. Therapeutic monitoring is especially important in animals receiving concurrent therapy with such drugs (Table 103-5). In dogs treated with cyclosporine (2 to 5 mg/kg PO q24h), concurrent ketoconazole administration (5 to 15 mg/kg q24h) can be used to decrease the required dose of cyclosporine, with considerable resultant cost savings. This strategy has primarily been used in dogs with perianal fistulas and dogs undergoing organ transplantation; however, it could also be considered in other diseases for which cyclosporine is indicated, although the effectiveness is unproven. Therapeutic monitoring of the cyclosporine concentration is important when using this strategy.

Adverse effects of cyclosporine include gastrointestinal disturbance, predisposition to infection, gingival hyperplasia, papillomatosis, and increased shedding of the haircoat. A dermatosis from atypical staphylococcal infection (psoriasiform lichenoid–like dermatosis) has also been reported in dogs treated with cyclosporine. Affected dogs improved after antibiotic therapy and a decreased dose of cyclosporine. At the doses used to treat atopic dermatitis (5 mg/kg PO q24h), no difference in prevalence of bacterial infection was demonstrated between dogs treated with prednisone and those treated with cyclosporine. The risk of infection is increased in dogs treated with higher doses of cyclosporine, such as those used to prevent transplant rejection (20 mg/kg PO q24h) and when cyclosporine is combined with other immunosuppressive drugs such as prednisone and azathioprine.

#### **VINCRISTINE**

Vincristine is an alkaloid derived from the periwinkle plant used as an antineoplastic and immunosuppressive agent. Vincristine binds to the microtubular structural protein tubulin, which is abundant within platelets. At low doses the drug causes a transient increase in circulating platelet numbers; at higher doses it can cause myelosuppression and thrombocytopenia. Proposed mechanisms for increased platelet numbers in normal dogs include stimulation of



### Immunosuppressive Drugs Used in Treatment of Immune-Mediated Diseases in Dogs and Cats

DRUG	DOSE (DOG)	DOSE (CAT)	ADVERSE EFFECTS	RECOMMENDED MONITORING
Prednisone	2-4 mg/kg/day	2-8 mg/kg/day	Signs of hyperadrenocorticism, gastrointestinal ulceration, predisposition to infection	History and physical examination, CBC, biochemical panel; monitor parameters of disease progression
Azathioprine	2 mg/kg/day	Not recommended	Bone marrow suppression, gastrointestinal upset, hepatotoxicity, pancreatitis	CBC, platelet count, liver enzymes biweekly for 2 months, then monthly
Chlorambucil	0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen	0.1-0.2 mg/kg PO q24h initially then q48-72h	Myelosuppression	CBC and platelet count weekly initially; may decrease to biweekly or monthly once stable
Cyclophosphamide	50 mg/kg/day PO for 4 out of 7 days or 200 mg/kg IV once a week	2.5 mg/kg/day PO for 4 out of 7 days or 7 mg/kg IV once a week	Bone marrow suppression, gastrointestinal upset, sterile hemorrhagic cystitis (rare in cats)	CBC, liver enzymes weekly for 2 months, then monthly; urinalysis biweekly
Cyclosporine	5 mg/kg q24h to 10 mg/kg q12h. Start at lower end of dose for microemulsified products (Neoral); lower doses of 1-2.5 mg/kg q12h if in conjunction with ketoconazole (see Table 103-4)	0.5-3 mg/kg q12h (microemulsified products); lower trough concentrations recommended in cats (250-500 ng/mL)	Gastrointestinal upset, infection, gingival hyperplasia, papillomatosis, increased shedding	CBC and biochemical panel monthly
Vincristine	0.02 mg/kg IV as a single dose for treatment of IMT	NA	Myelosuppression, thrombophlebitis if allowed to extravasate outside vein	Daily CBC and platelet count to monitor response of platelets
Danazol	5 mg/kg PO q12h	5 mg/kg PO q12h	Hepatotoxicity, virilization, weight gain, lethargy	CBC and biochemical panel monthly
hIVIG	0.25-1.5 g/kg as an IV infusion over 6-12 hours (one dose only)		Vomiting, mild thrombocytopenia in normal dogs	Monitor animal during administration by frequent TPR measurements, CBC and platelet count for disease monitoring

CBC, Complete blood count; NA, not applicable; TPR, total parenteral nutrition; IMT, immune-mediated thrombocytopenia; hIVIG, human intravenous immunoglobin.

thrombopoiesis by circulating thrombopoietic factors (perhaps by concealing platelets from the thrombopoietic regulatory system) or by inducing acute fragmentation of mature megakaryocytes. In immune-mediated thrombocytopenia, in which stimulation of thrombopoiesis is already

maximal, the mechanisms for increased platelet numbers are most likely increased platelet release from the bone marrow and impaired platelet destruction from inhibition of phagocytosis, or interference with antibody binding to platelets. Decreased antibody synthesis seems less likely considering



TABLE 103-4

# Selected Studies of Dosing Recommendations and Therapeutic Monitoring for Dogs Treated with Cyclosporine

REFERENCE	NUMBER OF CASES	PRODUCT USED	EFFECTIVE DOSE	CLINICAL INDICATION	TARGET THERAPEUTIC RANGE (TROUGH)*	INITIAL RESPONSE RATE
Mathews 1997	20	Sandimmune	5 mg/kg q12h	Perianal fistulas	400-600 ng/mL	85%
Griffiths 1999	6	Neoral	7.5 mg/kg q12h	Perianal fistulas	400-600 ng/ml	5/6
Olivery 2002	31	Neoral	5 mg/kg q24h	Atopic dermatitis	Not reported	61%
Mouatt 2002	16	Neoral	0.5-1.0 mg/kg q12h with ketoconazole 10 mg/kg q24h	Perianal fistulas	>200 ng/mL	93%
Patricelli 2002	12	Neoral	2.5 mg/kg q12h or 4 mg/kg q24h with ketoconazole 5- 11 mg/kg q24h	Perianal fistulas	400-600 ng/mL	8/12
O'Neill 2004	19	Neoral	0.5-2.0 mg/kg q12h with ketoconazole 5.3-8.9 mg/kg q12h	Perianal fistulas	400-600 ng/ml	100%
Hardie 2005	26	Neoral	4 mg/kg q12h	Perianal fistulas	Not measured	69%
Steffan 2005	268	Atopica	5 mg/kg q24h	Atopic dermatitis	Not measured	58%
Allenspach 2006	14	Atopica	5 mg/kg q24h	Inflammatory bowel disease	Peak concentrations 699 ± 326 ng/mL	12/14

<sup>\*</sup>Except where indicated.



TABLE 103-5

Pharmacokinetic Interactions with Cyclosporin A (CSA)

EFFECT OF THE CONCOMITANT THERAPY ON CSA CONCENTRATION	WELL-DOCUMENTED REPORT OF INTERACTION WITH MARKED EFFECTS ON BLOOD LEVELS	ANECDOTAL REPORTS OF INTERACTION	DOCUMENTED EVIDENCE OF ABSENCE OF INTERACTION
Increase of concentrations	Ketoconazole Fluconazole Itraconazole Itraconazole Diltiazem Erythromycin Clarithromycin Norfloxacin Phenytoin Metoclopramide Vitamin E (with Sandimmune)	Nafcillin Estradiol	
No change of concentrations			Methylprednisolone Cimetidine Vitamin E (with Atopica) Nonsteroidal antiinflammatory drugs Fluoroquinolones* β-Lactam antibiotics
Decrease of concentrations	Trimethoprim sulfonamides	Clindamycin	p Edelani dimbiones

Reprinted from Guaguere E et al: A new drug in the filed of canine dermatology, Vet Dermatol 15:61, 2004. Drugs in italics documented in dogs.

Text in **bold**, increase by >100%.

Regular text, increase or decrease by 50% to 100%.

<sup>\*</sup> Except norfloxacin.

the short time course for the increase in platelet count. Disruption of structure and function of platelets has been reported after exposure to vincristine in vitro and in vivo in dogs with lymphoma; however, the clinical significance of this finding is unclear.

The major indication for vincristine in treatment of immune-mediated disease is as an adjunctive therapy for ITP. Vincristine is administered at 0.02 mg/kg IV as a single dose in addition to treatment with glucocorticoids. Vincristine-treated dogs with ITP have a more rapid increase in platelet number and shorter duration of hospitalization than dogs treated with prednisone alone. The advantages of vincristine are that it is readily available and inexpensive. Although bone marrow suppression may occur at higher doses, this has not been reported at the low single dose used for treatment of immune-mediated thrombocytopenia. Care should be taken during intravenous administration because the drug is highly caustic if allowed to extravasate outside the vein.

#### DANAZOL

Danazol (Danocrine) is an attenuated synthetic androgen that has been used as an immunomodulating drug in dogs. In theory androgens suppress the immune response, and in people with immune-mediated hemolytic anemia and immune-mediated thrombocytopenia danazol has been found to decrease the amount of immunoglobulin and complement on the surface of RBCs and platelets. Isolated case reports have also suggested a beneficial effect in dogs with IMHA and thrombocytopenia, but confounding effects of other drugs occurred in both reports. In a double-blind study of danazol treatment in dogs with IMHA also treated with prednisone and azathioprine, no beneficial effect of danazol could be demonstrated. Side effects of danazol in dogs are uncommon but include hepatotoxicity, virilization (of females), weight gain, and lethargy. The recommended dose for danazol is 5 mg/kg q12h; however, no good evidence currently exists to support the use of this drug for treatment of immune-mediated diseases in dogs and cats.

### HUMAN INTRAVENOUS **IMMUNOGLOBULIN**

Human intravenous immunoglobulin (hIVIG) is a preparation of polyspecific immunoglobulin G (IgG) obtained from the plasma of a large number (more than 1000) of healthy human blood donors. hIVIG is available either as a solution or a lyophilized product, and a wide range of concentrations and vial sizes are available (5% to 10%, 1- to 12-g vials). Numerous commercial products are available and vary in price and availability (e.g., Gammagard S/D, Baxter Healthcare Corporation, Deerfield, Ill.; Gamimune N, Bayer Pharmaceuticals, Leverkusen, Germany). Human hIVIG is the treatment of choice for immune-mediated thrombocytopenic purpura and is also used for the treatment of a wide variety of other immune-mediated diseases in human beings. The mechanism(s) by which hIVIG modulates the immune system is unknown. In dogs the primary mechanism of hIVIG is hypothesized to be blockade of Fc receptors on mononuclear phagocytes, thereby inhibiting phagocytosis. Other potential mechanisms include decreased production of autoantibodies, possibly from effects of anti-idiotypic antibodies in hIVIG, functional modulation of T cells, decreased natural killer cell activity, blockade of complement-mediated cell damage, and modulation of the release and function of proinflammatory cytokines.

hIVIG has been used in veterinary medicine to treat immune-mediated hemolytic anemia, pure red cell aplasia, myelofibrosis, ITP, erythema multiforme, pemphigus foliaceus, and toxic epidermal necrolysis, although prospective studies evaluating the efficacy of hIVIG have yet to be performed in any of these diseases. Doses recommended for use in dogs range from 0.25 to 1.5 g/kg administered as an intravenous infusion over 6 to 12 hours. The potential limitation of treatment of dogs and cats with hIVIG is that administration of an infusion containing human protein could lead to sensitization and potential anaphylaxis if the treatment is repeated. However, no reports of anaphylactic reactions have yet been reported despite administration of the products at least twice (and in one case multiple times) in some dogs and cats. To date no clinically significant side effects have been reported in dogs or cats treated with hIVIG, although a high rate of thromboembolism was reported in one study of dogs with IMHA treated with hIVIG (Scott-Moncrieff et al., 1997). Whether this was related to the underlying disease or the treatment was not clear. Risk of thromboembolism is also a concern in people treated with hIVIG, especially in those with other risk factors for thromboembolism. Mild thrombocytopenia and occasional vomiting have been reported in normal dogs treated with hIVIG. The major limitation of hIVIG treatment is the expense, which has limited prospective studies of this mode of therapy in veterinary medicine, hIVIG is currently most commonly used as a rescue agent in dogs with immune-mediated diseases that are not responding to conventional immunosuppressive agents. Because of the rapid but short-acting effect of hIVIG on phagocytosis, the most logical use is as a bridge to suppress phagocytosis in diseases such as IMHA and ITP while waiting for other immunosuppressive drugs to become effective; however, clinical studies are currently lacking.

#### PENTOXIFYLLINE

Pentoxifylline belongs to the methylxanthine drug class and is a derivative of theobromine. Despite this derivation the drug does not have cardiac or bronchodilatory effects. The major properties of the drug relate to its effects on the immune system and blood viscosity. By mechanisms that are unclear, pentoxifylline improves the deformability of RBCs.

Pentoxifylline also has a number of immunomodulating effects, including inhibition of IL-1, IL-6, and tumor necrosis factor-α as well as inhibition of B- and T-cell activation. The pharmacokinetics of pentoxifylline have been described in the dog, and the current dose recommendation is 15 mg/kg PO q8h. In veterinary medicine pentoxifylline has primarily been used for the management of cutaneous immunemediated diseases, including dermatomyositis, SLE, and various forms of vasculitis. Whether the drug might be beneficial in other immune-mediated diseases is still to be determined. Adverse side effects in dogs are uncommon but may include vomiting, diarrhea, bone marrow suppression, and flushing.

#### **SPLENECTOMY**

Splenectomy is an adjunctive therapy that has been recommended in the management of hematologic immune-mediated diseases such as IMHA and ITP. Splenectomy is theorized to decrease the number of phagocytic mononuclear cells available for phagocytosis of antibody-coated RBCs and platelets. It is typically recommended in dogs with IMHA and ITP resistant to medical therapy. In dogs with relapsing ITP good evidence supports the merits of splenectomy in the subset of dogs with ITP that relapses after tapering of prednisone and azathioprine therapy. The merits of splenectomy in dogs with IMHA are less clear. Some case reports suggest that some dogs have better control of disease after splenectomy, but in other cases no benefit occurred. One concern regarding splenectomy in dogs with IMHA is that the spleen is an important site of extramedullary hematopoiesis, so splenectomy decreases the regenerative response. In addition, most dogs with IMHA are not good candidates for a major surgical procedure such as splenectomy.

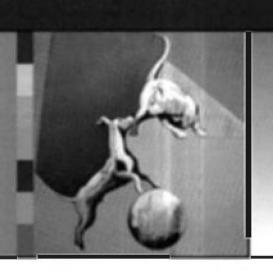
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# CHAPTER 104

# Common Immune-Mediated Diseases



# CHAPTER OUTLINE

IMMUNE-MEDIATED HEMOLYTIC ANEMIA
PURE RED CELL APLASIA
IMMUNE-MEDIATED THROMBOCYTOPENIA
IMMUNE-MEDIATED NEUTROPENIA
IDIOPATHIC APLASTIC ANEMIA
POLYARTHRITIS
SYSTEMIC LUPUS ERYTHEMATOSUS
GLOMERULONEPHRITIS
ACQUIRED MYASTHENIA GRAVIS
IMMUNE-MEDIATED MYOSITIS

Masticatory Myositis Polymyositis Dermatomyositis

# IMMUNE-MEDIATED HEMOLYTIC ANEMIA

#### Etiology

Immune-mediated hemolytic anemia (IMHA) is a clinical syndrome in which anemia results from the accelerated destruction of red blood cells (RBCs) by immune-mediated mechanisms (see Chapter 83). IMHA is the most common cause of hemolytic anemia in dogs but is much less common in cats. In primary IMHA (true autoimmune hemolytic anemia) antibodies are directed against RBC membrane antigens. These antigens have not been well characterized in the dog or cat, but antibodies directed against spectrin, band 3, and the family of erythrocyte membrane glycoproteins, known as glycophorins, have been identified. True autoimmune hemolytic anemia may also be a manifestation of systemic lupus erythematosus (SLE). In secondary IMHA an underlying disease is identified as a precipitating factor for the immune-mediated hemolytic process. Examples of causes of secondary IMHA include infection and neoplastic diseases (Box 104-1). Secondary IMHA may also occur after exposure to certain drugs, venoms, and possibly vaccines. Most studies in dogs suggest that primary autoimmune

hemolytic anemia is more common than the secondary form, although the frequency of identification of a secondary cause likely depends in part on how thoroughly the clinician searches for it. Secondary IMHA is more common than primary IMHA in cats.

The most common antibody classes identified on the RBC in both dogs and cats with IMHA are immunoglobulin (Ig) G and IgM, with IgA being least common. Complement is usually also present on the RBC. In secondary IMHA antibodies may be directed against antigens that adsorb to the RBC membrane or against a microbial antigen combined with a self-determinant, with the RBCs destroyed as an "innocent bystanders." Alternatively, previously hidden membrane antigens may be exposed by membrane damage from microbes or toxins, or microbial and drug antigens may be cross-reactive with self-determinants. Lastly, nonspecific activation of lymphocytes can result in formation of self-reacting lymphocytes in any chronic inflammatory process.

Recent vaccination has been implicated in the pathogenesis of IMHA. The occurrence of IMHA within 2 to 4 weeks of vaccination has been a clinical observation of concern to many owners and veterinarians. In one study of 58 dogs with IMHA, 26% of dogs had been vaccinated within 4 weeks of developing IMHA compared with a control group presenting for other disorders in which no increase in frequency of vaccination in the previous 4 weeks was observed (Duval et al., 1996). Mortality rates between the dogs that had been recently vaccinated and those that had not were not significantly different. In a later study that compared 72 dogs with IMHA to a control group, a temporal association between vaccination and development of IMHA was not identified (Carr et al., 2002). The importance of vaccination in the etiology of IMHA remains unclear.

IMHA clearly has a genetic predisposition, with the disease recognized more frequently in certain breeds (Box 104-2). The Cocker Spaniel appears to be the breed at greatest risk, accounting for as many as one third of cases. The presence of dog erythrocyte antigen 7 is associated with a protective effect in Cocker Spaniels (Miller et al., 2004). Female dogs and neutered dogs are overrepresented, suggesting a possible hormonal influence.



### BOX 104-1

# Infectious Diseases Implicated as Causing IMHA in Dogs

#### Dogs

- Dirofilariasis
- Hemotrophic mycoplasmosis
- Ehrlichia canis infection
- Anaplasma phagocytophilum infection
- Leishmaniasis
- Babesiosis
- Chronic bacterial infection

- Hemotrophic mycoplasmosis
- Feline infectious peritonitis
- Feline leukemia virus
- Chronic bacterial infection

IMHA, Immune-mediated hemolytic anemia.



# BOX 104-2

#### Dog Breeds at Increased Risk of IMHA

- Cocker Spaniel
- Bichon Frise
- Miniature Pinscher
- Miniature Schnauzer
- English Springer Spaniel
- Rough-Coated Collie
- Finnish Spitz

IMHA, Immune-mediated hemolytic anemia.

In IMHA the presence of antibody and/or complement on the RBC ultimately results in intravascular or extravascular hemolysis (see Chapter 83). Extravascular hemolysis is more common than intravascular hemolysis, is typically a less-acute process, and is commonly accompanied by spherocytes and hyperbilirubinemia (Figs. 104-1 and 104-2). Although hyperbilirubinemia is a common feature of IMHA, it does not occur in all cases and lack of hyperbilirubinemia does not rule out IMHA. Little clinical significance can be attributed to the relative proportions of conjugated and unconjugated bilirubin on the biochemical panel. Factors that determine the presence and severity of hyperbilirubinemia include the rate of hemolysis as well as hepatic function. In dogs with IMHA, hepatic function may be compromised by hypoxia and hepatic necrosis. In one study of 34 dogs that died of IMHA, 53% had moderate to severe centrilobular hepatic necrosis at necropsy (McManus et al., 2001).

#### **Clinical Features**

Dogs with primary IMHA are typically young to middleaged adults, with a reported age range of 1 to 13 years and a

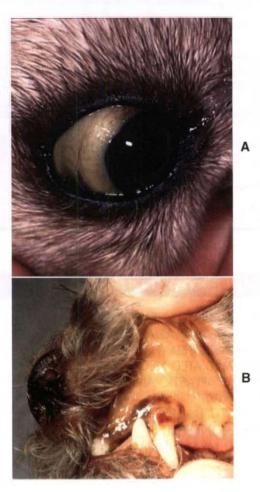


FIG 104-1 Mixed-breed dog with moderate icterus of the sclera (A) and the oral mucous membranes (B).

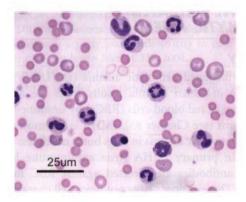


FIG 104-2 Photomicrograph of a blood smear demonstrating presence of spherocytes.

median age of 6 years. Females and neutered dogs of both sexes appear predisposed compared with sexually intact male dogs, and several breeds are overrepresented (see Box 104-2). Cats with primary IMHA tend to be younger than dogs, with a median age of 2 years. Males are slightly overrepresented, with no influence of neuter status (Kohn et al., 2006).



BOX 104-3

Historic and Physical Examination Findings in Dogs and Cats with IMHA

DOGS	CAT5
History	
Lethargy Angrexia	Lethargy Anorexia
Pallor	Pallor
Icterus	Icterus
Vomiting	Vomiting
Collapse	Pica
Weakness	
Physical Examination (Addition	onal Findings)
Systolic heart murmur	Systolic heart murmur
Pyrexia	Pyrexia
Tachycardia	Hypothermia
Tachypnea	Lymphadenomegaly
Pallor	Pallor
Icterus	Icterus
Splenomegaly Hepatomegaly	
Abdominal pain	
Abdominar bani	

IMHA, Immune-mediated hemolytic anemia.

Common clinical signs of IMHA are listed in Box 104-3. The duration of clinical signs before presentation to the veterinary hospital is typically short in both dogs and cats, with a median of 4 days. Seasonal increases in diagnosis of IMHA have been reported, although the findings are not consistent among studies. The majority of reports suggest an increased frequency of IMHA during the warmer months of the year.

#### Diagnosis

Diagnosis of IMHA relies on identifying abnormalities consistent with hemolytic anemia on a complete blood count (CBC), serum biochemistry panel, and urinalysis (Box 104-4) followed by identification of antibodies directed against the RBC membrane. Further diagnostic testing is then directed at establishing whether a secondary underlying cause for IMHA can be identified.

The first requirement for making a diagnosis of IMHA is the presence of anemia. The anemia is typically moderate to marked (median hematocrit of 13%) and is usually regenerative, although in approximately 30% of dogs and more than 50% of cats the anemia is nonregenerative. Reasons for nonregenerative anemia in IMHA include an acute onset and presentation before the bone marrow has had time to respond (typically takes 3 to 5 days for maximal regenerative response) and the presence of antibodies directed against bone marrow precursors. In the latter situation, reticulocytes are destroyed before they enter the peripheral circulation. In the absence of a regenerative response, a rapid fall in the hematocrit with little change in the serum total protein or



#### BOX 104-4

Abnormalities on the CBC and Serum Chemistry Profile in Dogs with IMHA

#### CBC

- Anemia
- Polychromasia
- Autoagglutination
- Spherocytosis
- Ghost cells
- Evidence of inflammation (increased neutrophils, bands, metamyelocytes, monocytes)
- Thrombocytopenia

#### **Biochemical Profile**

- Hemoglobinemia
- Hemoglobinuria
- Hyperbilirubinemia
- Hyperbilirubinuria
- Increased alanine aminotransferase
- Increased alkaline phosphatase

CBC, Complete blood cell count; IMHA, immune-mediated hemolytic anemia.

albumin concentration should be considered suspicious for hemolysis. In anemia caused by decreased RBC production from the bone marrow, the hematocrit should not decrease by more than approximately 1% per day, whereas in blood loss anemia the drop in the hematocrit is usually accompanied by a concurrent decrease in the total protein or albumin (Table 104-1).

Most dogs with IMHA also have an inflammatory leukogram, often with a shift toward immature cells; thrombocytopenia; and abnormalities of the coagulation system, including prolongation of both the activated partial thromboplastin time (aPTT) and prothrombin time, elevations in D-dimer and fibrinogen degradation products, decreased antithrombin, and increased fibrinogen. Reasons for thrombocytopenia include the presence of antibodies directed against platelets as well as RBCs (Evans syndrome), disseminated intravascular coagulation, or sequestration in the spleen.

Identification of autoagglutination or spherocytosis (2+ or more) on a blood smear is considered definitive evidence of antibody-mediated RBC hemolysis (Fig. 104-3). Autoagglutination is detected by macroscopic or microscopic examination of the blood smear and is generally considered diagnostic for IMHA. Agglutination must be distinguished from rouleaux formation (see Chapter 83).

Spherocytes are formed by partial removal of antibody-coated RBC membranes by macrophages (see Fig. 104-2). This results in a loss of the normal discoid shape, decreased size, and loss of central pallor. Spherocytes are more rigid and less deformable than normal RBCs and are removed when they pass through the spleen. Spherocytes are readily identified in the dog but difficult to recognize in cats because of the lack of significant central pallor in their normal RBCs.



### TABLE 104-1

### Expected Changes on the CBC in Different Causes of Anemia

TYPES	RATE OF DECREASE OF HEMATOCRIT	RETICULOCYTE COUNT	SERUM PROTEINS	EVIDENCE OF INFLAMMATION ON CBC	THROMBOCYTOPENIA
Hemolytic anemia	Fast Slow	High	No change	Yes	Yes (mild to severe)
Nonregenerative anemia Blood loss anemia	Fast	Low High	No change Decreased	No No	Depends on cause Yes (mild only)

CBC, Complete blood cell count.

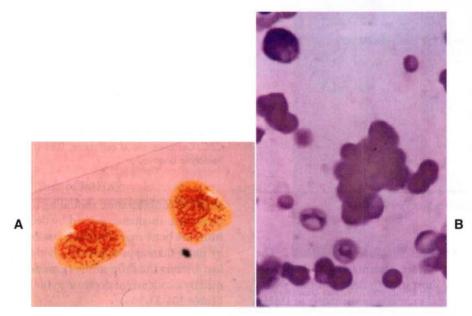


FIG 104-3
Blood smear showing gross (A) and microscopic (B) agglutination. Note the three-dimensional clustering of red blood cells on the microscopic view.

Spherocytes are considered a hallmark morphologic change in IMHA, and when present in sufficient numbers (2+ or greater) may be regarded as diagnostic for IMHA in dogs. Of note, low numbers of spherocytes (1+) may be observed on a blood smear when damage to the RBC is nonimmune (e.g., zinc toxicosis, hypophosphatemia, oxidative damage, rickettsial diseases, neoplasia, microangiopathic anemia). Techniques for quantitation of spherocyte numbers are typically semiquantitative (Table 104-2). In retrospective studies approximately 90% of dogs with IMHA have spherocytes present on the blood smear; however, low numbers may be present in dogs with per-acute hemolysis. Ghost cells are remnant membranes of RBCs that have undergone intravascular lysis. Lysis can be induced by immune- or nonimmune-mediated mechanisms, so ghost cells are not diagnostic for IMHA.

The direct Coombs test with polyvalent antisera is the most commonly used diagnostic test for IMHA when autoagglutination or spherocytosis is not present; however, this test is neither particularly sensitive nor specific for confirm-

ing a diagnosis of IMHA. A positive Coombs test indicates that antibody, complement, or both are on the surface of the RBC but does not mean that the antibody is directed specifically against the RBC membrane or that the antibody is causing hemolysis. Approximately 60% to 80% of canine patients with IMHA have a positive Coombs test. Conversely, a positive Coombs test can occur in a variety of other inflammatory diseases causing false-positive results (see Chapter 102).

A search for secondary causes of IMHA should always be undertaken in a dog or cat with IMHA because the underlying disease may influence management strategy and prognosis. Potential secondary causes of IMHA are listed in Table 104-3. The diagnostic approach to ruling out secondary IMHA includes a thorough history of drug, vaccine, and toxin exposure; detailed physical examination, including rectal, ophthalmologic, and neurologic examinations; tests for specific infectious diseases; investigation into causes of chronic antigenic stimulation; and a search for evidence of neoplasia. Diagnostic tests to consider in addition to a CBC, biochemical panel, and urinalysis include urine culture,

abdominal and thoracic radiographs, abdominal ultrasound, bone marrow cytology or histopathology (or both if the anemia is nonregenerative), and appropriate titers for infectious diseases.

Results of bone marrow evaluation in dogs with nonregenerative primary IMHA typically reveal erythroid hyperplasia with a low mycloid/erythroid (M/E) ratio, although maturation arrest at the rubricyte or metarubricyte stage may also be observed. Some dogs initially suspected to have IMHA based on the presence of spherocytosis or a positive Coombs test have pure red cell aplasia. Myelofibrosis can be detected on bone marrow core biopsy in many dogs with nonregenerative IMHA. In dogs with myelofibrosis, collection of adequate bone marrow elements by aspiration cytology is difficult. Myelofibrosis is likely a secondary response to bone marrow injury and may resolve in dogs that respond to treatment.

In dogs without the classic morphologic changes of immune-mediated hemolysis (regenerative anemia, autoagglutination, spherocytes), confirming a diagnosis of IMHA may be challenging. A positive direct Coombs test should be



TABLE 104-2

Semiquantitative Scoring System for Numbers of Spherocytes on a Slide

APPROXIMATE NUMBER OF					
ASSIGNED SCORE					
1+					
2+					
3+					

interpreted cautiously in such cases because false-positive results may occur. The logical approach is to rule out other causes of anemia (see Chapter 83) and use the Coombs test and other indications of hemolysis as supporting evidence of IMHA if no other cause of anemia is identified.

#### **Treatment**

Choosing an appropriate treatment regimen for dogs with IMHA is a frustrating task for the clinician (Fig. 104-4). Lack of prospective studies of treatment efficacy, the poor prognosis associated with the disease, and the high cost of treatment and supportive care are some reasons for this frustration. In addition, serious complications such as pulmonary thromboembolism and disseminated intravascular coagulation are relatively common occurrences but hard to predict in individual patients. Because of the lack of prospective studies of treatment efficacy, recommendations for approach to treatment in dogs with IMHA are based primarily on clinical experience rather than objective data.

When planning the management of a dog with IMHA, the goals of treatment should include prevention of RBC hemolysis, alleviation of tissue hypoxia by blood transfusion, prevention of thromboembolism, and provision of supportive care.

**Prevention of hemolysis.** Immunosuppressive drugs are the key for prevention of RBC hemolysis in dogs with IMHA. The mechanism of action and adverse effects associated with the use of various immunosuppressive drugs recommended for use in dogs and cats with autoimmune disorders are discussed in Chapter 103.

High doses of glucocorticoids are the first line of treatment for controlling RBC hemolysis in dogs with IMHA. In dogs that can tolerate oral medication, prednisone at a dose of 1 to 2 mg/kg PO q12h is the corticosteroid of choice. The



TABLE 104-3

Secondary Causes of IMHA in Dogs and Cats

	EXAMPLES	DIAGNOSTIC TESTS INDICATED
Neoplasia	Lymphoma	Abdominal/thoracic radiographs
•	Hemangiosarcoma	Abdominal ultrasound
	Leukemia	Bone marrow aspirate
	Malignant histiocytosis	Lymph node aspirates
Infection (see Box 104-1)	Feline leukemia virus	Serology
	Hemotrophic mycoplasmosis	IFA/PČŘ
	Dirofilaria immitis	Serology
		Thoracic radiographs
		Urinary tract infection
Chronic inflammation	Prostatitis	Urine culture
	Colitis	Ultrasound of urinary tract
	Discospondylitis	Colonoscopy
	Polyarthritis <sup>*</sup>	Spinal radiographs
	,	Synovial fluid collection and radiographs
Exposure to drugs vaccines or toxins	Antibiotics (sulfonamides, β-lactam antibiotics)	Detailed history

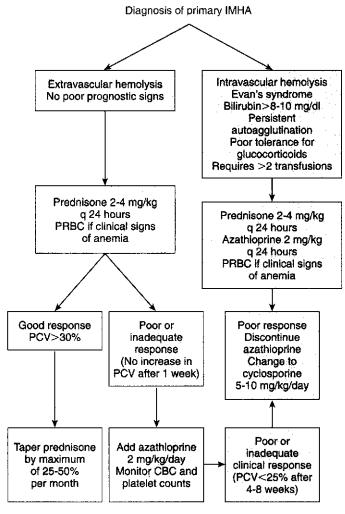


FIG 104-4 Flow diagram showing approach to treatment in dogs with immune-mediated hemolytic anemia.

higher end of the dose range is recommended as a starting dose except in large breed dogs (more than 30 kg). Most dogs that will respond to prednisone show some improvement within the first 7 days of treatment, but the full therapeutic effect may not be evident until 2 to 4 weeks after initiation of treatment. Once the hematocrit increases above 30%, the dose may be decreased to 1 mg/kg q12h. Subsequently the dose is tapered by a maximal rate of 25% to 50% per month over a 3- to 6-month period depending on the hematocrit and severity of side-effects. If after 6 months the prednisone dose is tapered to a low every-other-day dose and the disease is in remission, discontinuation of medication should be attempted. A CBC and reticulocyte count should be performed before and 2 weeks after any change in immunosuppressive therapy. Indications of resolution of the hemolytic process in addition to improvement in the anemia include a negative Coombs test (if it was initially positive), resolution of autoagglutination, resolution of spherocytosis, normalization of the reticulocyte count, and improvement in the leukogram with resolution of inflammation.

Most cats with IMHA respond to prednisone alone and rarely have problems with the adverse effects of glucocorticoids. In the occasional cat that needs an additional immunosuppressive drug to treat IMHA, treatment with chlorambucil, cyclophosphamide, or cyclosporine should be considered. Not enough published information exists on which to base a recommendation of one drug over another. Azathioprine is not recommended in cats because of the risk of unacceptable side effects (see Chapter 103).

Some dogs with IMHA do not respond to glucocorticoid treatment alone, or the dose of prednisone cannot be tapered enough for adequate resolution of adverse effects of glucocorticoids. In those cases an additional cytotoxic drug should be added to the treatment regimen. One common clinical dilemma is whether all dogs with IMHA should be treated with an additional immunosuppressive drug early in the course of treatment, or whether waiting and identifying which dogs are likely to benefit is more appropriate. The advantage of starting another immunosuppressive drug early is that no time is lost waiting to identify which patients will respond to glucocorticoid treatment alone. The disadvantages include the risk of adverse effects and the lack of evidence of benefit in all cases. In studies at Purdue University approximately 20% of dogs with IMHA are ultimately treated with another immunosuppressive drug in addition to prednisone. Use of more than one additional immunosuppressive drug at any one time is not recommended because of the potential for severe immunosuppression and resultant susceptibility to infection.

The choice for additional immunosuppression varies among clinicians. Viable options include azathioprine, cyclophosphamide, and cyclosporine. In our hospital azathioprine is added early in the course of treatment in dogs that do not respond within 5 to 7 days of initiating glucocorticoid treatment and in dogs that require more than two transfusions of blood or a hemoglobin-based oxygen carrier. Azathioprine is also used in dogs known to have a poor tolerance of the side-effects of glucocorticoids (e.g., large-breed dogs) and in those with other poor prognostic indicators (e.g., intravascular hemolysis, serum bilirubin level greater than 8 to 10 mg/dL, persistent autoagglutination, Evans syndrome). The recommended starting dose for azathioprine in dogs is 2 mg/kg q24h. Once control of IMHA is attained, azathioprine should be continued at the same dosage while the dose of prednisone is tapered. Azathioprine is then tapered slowly once the prednisone has been discontinued. If a relapse occurs, life-long prednisone, azathioprine, or both are recommended at the lowest dose that controls RBC hemolysis. CBC and hepatic enzymes should be monitored biweekly initially, then every 1 to 2 months in dogs treated with azathioprine.

Historically, cyclophosphamide has been recommended for treatment of dogs with severe acute IMHA. However, evidence is mounting that addition of cyclophosphamide does not improve outcome and that its use may be associated with a poorer prognosis in dogs with IMHA. Cyclophosphamide is usually reserved for dogs that do not tolerate oral drugs because of persistent vomiting or gastrointestinal

disease (cyclophosphamide can be administered intravenously; see Table 103-3) or because of expense (cyclosporine).

Cyclosporine is currently the preferred immunosuppressive drug for dogs that do not respond to prednisone and azathioprine. The cost of cyclosporine is a major deterrent to its use, and its potent immunosuppressive effects mandate frequent monitoring of the patient for infections. Interestingly, in a prospective study of 38 dogs with IMHA, no difference in survival was found between dogs treated with prednisone alone and those treated with prednisone and cyclosporine; however, most of the deaths occurred early before the effects of cyclosporine had likely reached maximal effect (Husbands et al., 2004). Cyclosporine appears to be relatively safe in dogs with IMHA, and clinical experience suggests that it is useful and effective in the treatment of dogs with IMHA that do not respond to prednisone or azathioprine. (For dosing and monitoring recommendations for cyclosporine, see Tables 103-3 and 103-4.)

Human intravenous immunoglobulin (hIVIG) has had beneficial effects in dogs with IMHA that are refractory to other therapy. Administration of hIVIG may be most useful early in the treatment of acute severe IMHA to control acute hemolysis while waiting for other immunosuppressive drugs to become effective. Cost is a deterrent to using hIVIG, and multiple treatments are not currently recommended because of the potential for sensitization to this human product, although dogs have been treated twice with no obvious deleterious effects.

**Blood transfusion.** Most dogs and cats with acute, severe IMHA need oxygen-carrying support while waiting for the anemia to improve. Oxygen supplementation alone is of limited benefit. The need for blood transfusion depends on the severity of anemia, the rapidity of onset and chronicity of the anemia, and the presence and severity of concur-

rent disease such as pulmonary thromboembolism and gastrointestinal blood loss. No specific hematocrit level is necessary as a transfusion trigger; rather, each patient should be considered individually. In general, transfusion should be considered when the dog has problems with tachycardia, tachypnea, anorexia, lethargy, or weakness while at rest. Most dogs with acute IMHA and a hematocrit level less than 15% have some degree of tissue hypoxia and will benefit from a blood transfusion regardless of how the dog appears to be doing clinically. Severe tissue hypoxia likely exacerbates the complications of IMHA, such as hepatic necrosis, disseminated intravascular coagulation, and thromboembolism.

Options for providing oxygen-carrying support include transfusion of packed RBCs (pRBCs) or a hemoglobin-based oxygen carrier (HBOC) such as Oxyglobin (Biopurc, Cambridge, Mass.). Transfusion of whole blood is acceptable but less ideal because the plasma component is not necessary and may increase the risk of transfusion reactions. Disadvantages of HBOC include the short duration of effect (74 to 82 hours at the 30-mL/kg dose) and the discoloration of serum caused by the transfused hemoglobin, which interferes with many analytes on the biochemical profile (see Table 104-4 for a list of valid analytes). In dogs with hematocrit levels less than 8%, HBOC alone will not provide adequate oxygencarrying support, and additional support with pRBCs or whole blood is recommended. (See Chapter 83 for more information about blood transfusions and HBOCs.)

**Prevention of thromboembolism.** Thromboembolic events (TEs) are a common complication and important cause of death in dogs with IMHA. TEs have been documented at necropsy in 29% to 80% of dogs with IMHA. Intravenous catheter placement and identification of certain laboratory abnormalities, such as thrombocytopenia, hyper-



TABLE 104-4

Valid Analytes by Instrumentation after Oxyglobin Administration (Plasma Hemoglobin = 4.0 g/dL)

(TABLE TOP)	HITACHI (ALL MODELS)	JOHNSON & JOHNSON EKTACHEM/VITROS	DUPONT DIMENSION	BECKMAN CX7/CX3
Sodium Potassium Chloride BUN CK Creatinine	Sodium Potassium Chloride BUN Creatinine Glucose ALT AST Calcium CK	Sodium Potassium Chloride BUN CK AST Calcium Magnesium Lipase Glucose	Sodium Potassium Chloride BUN LDH Calcium	Sodium Potassium Chloride BUN Calcium Glucose

This table reflects the analytes that would be unaffected by Oxyglobin (Biopure, Cambridge, Mass.) immediately after a dose of 30 mL/kg. There are no known interferences in the measurement of sodium, chloride, potassium, and BUN on these five instruments in the presence of Oxyglobin.

Reprinted from www.oxyglobin.com/downloads/Oxyglobin\_Pl.pdf. Accessed March 5, 2008.

BUN, Blood urea nitrogen; CK, creatine kinase; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

bilirubinemia, leukocytosis, and hypoalbuminemia, are associated with an increased risk of TE in dogs with IMHA. The pathogenesis of thrombus formation is unknown, and effective regimens for prophylaxis have not been established. Treatment options currently used for prevention of thromboembolic complications include heparin, lowmolecular-weight heparin, aspirin, or a combination of these modalities. The recommended starting dose for heparin in patients with IMHA is 200 to 300 U/kg q6h, and the dose is adjusted by measuring anti-Xa activity (0.35 to 0.7 U/mL) or, less ideally, monitoring the aPTT with the aim to prolong aPTT by 25% to 50% of baseline. (For a discussion of the use of low-molecular-weight heparin, see Chapter 12.) Low-dose aspirin (0.5 mg/kg q24h) has also been used to prevent thromboembolic complications in dogs with IMHA. Weinkle et al (2005) reported that dogs treated with a protocol that included prednisone, azathioprine, and lowdose aspirin had the longest survival times. (See Chapter 12 for more information on treatment and prevention of thromboembolism.)

**Supportive care.** Aggressive supportive care is critical to a good outcome in dogs with IMHA. Identification and treatment of underlying disease, detection of complications associated with immunosuppressive drug therapy, and good nursing care positively influence outcome. In addition to transfusion, fluid therapy should be administered in dogs with evidence of dehydration to improve tissue perfusion. In dehydrated dogs fluid therapy will decrease the measured hematocrit, but this does not change the total RBC mass. Fluid therapy should not be withheld because of fear of exacerbating anemia. In reality, fluid therapy reveals the true severity of the anemia.

Careful investigation and treatment of underlying disease in dogs with IMHA are important. Immunosuppressive therapy is usually still necessary in dogs with secondary IMHA. However, the duration of immunosuppression may be shorter if an underlying cause can be identified and treated. If an infectious disease is identified, addition of cytotoxic drugs (e.g., azathioprine, cyclophosphamide, chlorambucil) should be avoided.

Complications of immunosuppressive drug therapy include bone marrow suppression, infection, gastrointestinal ulceration, and iatrogenic hyperadrenocorticism. Gastrointestinal hemorrhage can contribute to anemia in dogs with IMHA, either from the gastrointestinal effects of high doses of glucocorticoids or concurrent thrombocytopenia, vasculitis, ischemia, or other concurrent disease. Recognition of occult gastrointestinal hemorrhage is important because the resulting anemia may be confused with a failure to respond to treatment for IMHA (see Chapter 83). Drugs used for treatment of gastrointestinal hemorrhage include gastrointestinal protectants such as sucralfate and H<sub>2</sub> blockers (e.g., famotidine).

### **Prognosis**

Reported mortality rates of dogs with primary IMHA range from 26% to 70%, with thromboembolism being the cause of death in at least 30% to 60% of cases. Other common causes of death include infection, disseminated intravascular coagulation, and failure to control anemia. Factors that clinically appear to confer a good prognosis in dogs with IMHA include a rapid response to treatment with glucocorticoids, ability to maintain the packed cell volume at greater than 25% to 30% with glucocorticoids alone, and identification of a treatable secondary cause. The prognosis is more guarded in dogs that require multiple drugs to control the disease and those with persistent autoagglutination, an elevated bilirubin concentration, marked thrombocytopenia, and severe leukocytosis. If a major TE does occur in a dog with IMHA, particularly if blood supply to a major organ is disrupted, the long-term prognosis is typically very poor. Contrary to popular opinion the prognosis in Cocker Spaniels with IMHA does not differ from that of other breeds. In approximately 60% of dogs with IMHA, medications can ultimately be discontinued after a slow tapering of the dose. The remaining dogs require long-term immunosuppressive therapy.

# **PURE RED CELL APLASIA**

Pure red cell aplasia (PRCA) is a rare disorder characterized by severe, nonregenerative anemia with marked depletion or absence of erythroid precursors in the bone marrow. In some cases evidence of concurrent peripheral RBC hemolysis is present, based on the presence of spherocytes and a positive antiglobulin test. Other cell lines are usually normal. The erythroid aplasia in PRCA is in contrast to the nonregenerative form of IMHA, in which there is erythroid hyperplasia or sometimes maturation arrest of the erythroid maturation sequence. PRCA is likely one end of the spectrum of IMHA, with acute peripheral hemolysis at the other end of this spectrum (Table 104-5). The affinity of circulating antibody for different erythroid precursors likely influences the level at which damage occurs in the bone marrow. As with IMHA, both primary and secondary forms of PRCA are recognized. Secondary causes of PRCA include treatment with recombinant human erythropoietin and parvovirus infection in dogs. Infection with feline leukemia virus subtype C is a cause of PRCA in cats.

Dogs with PRCA have a similar signalment and present with similar clinical signs as dogs with IMHA. Cats with primary PRCA are typically younger than dogs, with an age range of 8 months to 3 years. Dogs and cats with PRCA have severe, nonregenerative anemia; the platelet count and leukogram are typically normal. In contrast to IMHA the biochemical panel and urinalysis are also usually unremarkable, with no evidence of peripheral hemolysis. Low numbers of spherocytes are sometimes present in dogs with PRCA. The Coombs test is usually negative.

Diagnosis of PRCA is made by evaluation of a bone marrow aspirate and bone marrow core biopsy. In dogs with PRCA, erythroid precursors are rare or absent and the M/E ratio is quite high (more than 99:1). In contrast to dogs with nonregenerative IMHA, severe myelofibrosis is rare.



# Comparison of Regenerative IMHA, Nonregenerative IMHA, and PRCA in Dogs

	RATE OF DECREASE OF HEMATOCRIT	RETICULOCYTE COUNT	(% POSITIVE)	EVIDENCE OF INFLAMMATION ON CBC	THROMBOCYTOPENIA	BONE MARROW EVALUATION
Regenerative hemolytic anemia	Fast	High	60%-80%	Severe inflammatory leukogram in most dogs	Yes (60%)	Erythroid hyperplasia, myelofibrosis some cases
Nonregenerative anemia	Variable	Low	57%	Mild inflammation in 50% of dogs only	Rare	Erythroid hyperplasia, myelofibrosis common
PRCA	Slow	Low	Rarely positive	No .	No	Erythroid hypoplasia, myelofibrosis uncommon

IMHA, Immune-mediated hemolytic anemia; PRCA, pure red cell aplasia; CBC, complete blood cell count.

Treatment of PRCA is similar to IMHA. Most dogs with PRCA respond to prednisone alone. Azathioprine or cyclophosphamide may be necessary for a complete response in some dogs or may be added to allow tapering of the prednisone dose in dogs with unacceptable side effects of corticosteroid therapy. The time taken to achieve complete remission (2 to 6 months) is longer in dogs with PRCA compared with IMHA, and it is sometimes difficult to judge whether a particular protocol is failing or whether inadequate time has been allowed for the bone marrow to respond to treatment and begin to produce and release RBCs into the circulation. Sequential bone marrow evaluations should ideally be used to determine when to change the treatment protocol. A repeat bone marrow aspirate should be considered after 2 months of treatment if no improvement in the anemia is observed. Repeated transfusion of pRBCs or whole blood is necessary while waiting for a response to treatment. Dogs with PRCA do not typically have evidence of systemic inflammation and are not at increased risk of TEs, so anticoagulant treatment is not indicated. The prognosis for PRCA in dogs is better than for IMHA, with mortality rates being less than 20%. The major cause of death is euthanasia because of the high cost of supportive care. Response to treatment and mortality rates in cats with PRCA appears to be similar to dogs, although cats respond to treatment more quickly (1.5 to 5 weeks). See Chapter 83 for additional information on PRCA.

# IMMUNE-MEDIATED THROMBOCYTOPENIA

# Classification/Etiology

Immune-mediated thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) is a clinical syndrome in which thrombocytopenia results from antibody-mediated accelerated destruction of platelets. Immune-mediated thrombocytopenia is diagnosed in approximately 3% to 18% of cases of thrombocytopenia and is the most common cause of severe thrombocytopenia in dogs (Table 104-6). Immunemediated thrombocytopenia is classified as primary or secondary. In primary thrombocytopenia (true autoimmune thrombocytopenia) antibodies are directed against platelet antigens, presumably because of an underlying defect in immune regulation. Antibodies directed against platelet membrane glycoproteins IIb and IIIa have been identified as target antigens in dogs, although others may be important as well. Primary ITP is a common cause of thrombocytopenia in dogs but is rare in cats. Environmental factors suspected to precipitate ITP in some cases include stress, changes



#### Causes of Thrombocytopenia in Dogs and Cats

CAUSE	MECHANISM	DOGS	CATS	
Immune-mediated disease	ase Antibody mediated Primary ITP Secondary ITP		Secondary ITP Primary ITP	
Neoplasia	Antibody mediated	Lymphoma	Leukemia	
	Bone marrow suppression Myelophthisis	Hemangiosarcoma Leukemia Malignant histiocytosis Many others	Hemangiosarcoma Many others	
Infection	Antibody mediated	Ehrlichia canis	Feline leukemia virus	
	Bone marrow suppression Myelophthisis	Anaplasma phagocytophilum Anaplasma platys	Feline immunodeficiency virus	
	7 - 1	Rocky Mountain spotted fever Bartonellosis	Feline infectious peritonitis virus	
		Dirofilaria immitis	Feline panleukopenia virus	
		Angiostrongylus vasorum Distemper virus infection Bacteremia	Toxoplasmosis	
Exposure to drugs,	Antibody mediated	Antibiotics (trimethoprim/	Griseofulvin	
vaccines, or toxins	Bone marrow suppression	sulfadiazine, etc.)	Methimazole	
vaccinos, or ioxino	Idiosyncratic	Phenobarbital	111011111102010	
	, 2, 2, 2, 3, 1, 2, 2, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,	Primidone		
		Gold salts (auranofin)		
Disseminated intravascular	Platelet utilization	Neoplasia `	Neoplasia	
coagulation		Hepatic disease	Hepatic disease	
		Infection	Infection	
		Pancreatitis	Pancreatitis	

in environmental temperature, hormonal changes, vaccination, and surgery.

In secondary ITP antibody-mediated platelet destruction occurs as a result of an underlying inflammatory or neoplastic disease. Causes of secondary immune-mediated thrombocytopenia in dogs and cats are listed in Table 104-6. Immune-mediated thrombocytopenia may also be a component of SLE and may occur in conjunction with IMHA (Evans syndrome).

#### **Clinical Features**

Dogs with primary ITP range in age from 8 months to 15 years, with a median age of 6 years. Females are affected twice as often as males, and although any breed can be affected the Cocker Spaniel, Poodle (all varieties), German Shepherd dog, and Old English Sheepdog are overrepresented. Common findings include sudden onset of petechial and ecchymotic hemorrhages in the skin and mucous membranes, epistaxis, hematochezia, hematemesis, easy bruising, lethargy, weakness, and anorexia. Additional findings on physical examination may include melena, hematuria, hyphema, retinal

the oral mucous membranes.

hemorrhage, and pale mucous membranes (Fig. 104-5). Neurologic signs and blindness may occur from bleeding into the CNS and eye, respectively. Because rapid-onset, lifethreatening hemorrhage is rare in dogs with ITP, anemia is usually initially mild and slowly progressive unless IMHA is concurrent. As affected dogs become moderately to severely anemic, lethargy, exercise intolerance, tachypnea, tachycardia, and a heart murmur may be evident. In some dogs with ITP clinical signs of hemorrhage are not present and thrombocytopenia is an incidental finding on bloodwork performed for another reason. The platelets present in dogs with ITP are often larger and may be hemostatically more competent, which may explain why not all dogs with severe ITP bleed spontaneously. However, platelet dysfunction (impaired aggregation) has been documented in normal canine platelets after incubation with serum from dogs with ITP, suggesting that antibodies or other factors in the serum impair platelet function in some dogs with ITP. Certain breeds, such as the Cavalier King Charles Spaniel and the Greyhound, are known to have lower platelet counts than other dogs and do not appear to have increased risk of bleeding.



Photographs of three dogs with immune-modulated thrombocytopenia and ecchymotic hemorrhage. **A,** Note the ecchymotic hemorrhages in the skin of the abdomen. **B,** Note the hemorrhage into the anterior chamber of the eye. **C,** Note petechial hemorrhage in

#### Diagnosis

Because immune-mediated thrombocytopenia can occur in association with many other disorders (see Table 104-6 and Chapter 87), a diagnosis of primary ITP can only be made by ruling out other causes of thrombocytopenia. Dogs with ITP usually have severe thrombocytopenia (less than 50,000 platelets per  $\mu L$ ), and platelet fragments (microthrombocytosis) may be present on the blood smear. Platelet fragments are reported to be a specific but insensitive indication of ITP. Platelet fragments may be present as a result of immune injury or because larger platelets are preferentially removed from circulation. The presence of enlarged platelets on the blood smear supports the presence of increased bone marrow production of platelets, but this is not specific for a regenerative response because bone marrow injury may also cause enlarged platelets.

Diagnosis of ITP is confirmed by ruling out other cause of severe thrombocytopenia (see Table 104-6 and Chapter 87). Spurious thrombocytopenia from platelet clumping, other technical problems, and breed-related thrombocytopenia should be considered in dogs that do not have clinical signs of bleeding. In dogs with thrombocytopenia, examination of a bone marrow aspirate should be performed early in the diagnostic workup to rule out disorders such as myelophthisis, neoplasia, megakaryocytic aplasia, and aplastic anemia (see Chapter 87). Bone marrow aspiration and biopsy can be safely performed even in severely thrombocytopenic dogs because hemorrhage can be controlled with local pressure. In most dogs with ITP normal to increased numbers of megakaryocytes are present on a bone marrow aspirate. Decreased numbers of megakaryocytes in the bone marrow have been associated with a poorer prognosis in dogs with ITP. Megakaryocytic aplasia is a rare disorder in which aplasia of the megakaryocytic cell line results in severe thrombocytopenia. This disease may be a primary immunemediated disease or occur secondary to infections such as Ehrlichia canis and Borrelia burgdorferi. Immune-mediated megakaryocytic aplasia has a poor prognosis unless it is caused by underlying infection.

The presence of a positive assay for platelet-bound antibody (see Chapter 102) is highly sensitive but not specific for a diagnosis of ITP. A diagnosis of ITP is unlikely if the test result is negative. A positive test result is not specific for ITP because immune-mediated mechanisms are responsible for many causes of thrombocytopenia in dogs, including Babesia canis, Dirofilaria immitis, E. canis, myelodysplasia, SLE, drug reactions to trimethoprim sulfadiazine, and various forms of neoplasia.

#### **Treatment**

**Immunosuppression.** Immunosuppressive drugs are the key to treating ITP. High doses of corticosteroids block macrophage-mediated destruction of platelets and are the first line of treatment in dogs with ITP. Prednisone at a dose of 1 to 2 mg/kg q12h is the corticosteroid of choice. Treatment with one dose of vincristine (0.02 mg/kg IV) should also be considered early in the course of treatment for dogs

with severe ITP (platelet count less than 15,000/ $\mu$ L). Dogs treated with vincristine have a more rapid increase in platelet count and shortened duration of hospitalization compared with untreated dogs. Most dogs with ITP have a rapid response to prednisone or prednisone combined with vincristine, and in most cases the platelet count increases to more than 50,000 per  $\mu$ L within 7 days of treatment. Once the platelet count is in the reference range, the dose of prednisone can be slowly tapered. Because of the risk of relapse the dose should not be tapered more rapidly than 25% to 50% per month over a 3- to 6-month period. If after 6 months the prednisone dose has been tapered to a low everyother-day dose and the disease is in remission, discontinuation of medication should be attempted.

Azathioprine therapy should be considered in dogs that do not have an adequate response to prednisone alone (platelet count less than 100,00 per μL) or in whom the dose of prednisone cannot be tapered low enough to manage the adverse effects of glucocorticoids. The dose of azathioprine is 2 mg/kg q24h. If azathioprine is tolerated the dose should be continued while the dose of prednisone is tapered. Azathioprine is tapered slowly once prednisone has been discontinued. If a relapse occurs, life-long prednisone and/or azathioprine should be continued at the lowest dose that maintains the platelet count within the reference range. A platelet count should be performed before and 2 weeks after any change in immunosuppressive therapy. In some dogs with ITP maintaining the platelet count within the reference range is difficult without severe glucocorticoid side effects. In these dogs maintaining the platelet count greater than 100,000 per µL is acceptable because this level of thrombocytopenia is usually not associated with increased risk of bleeding. Other drugs that can be considered in dogs with refractory ITP include danazol, cyclophosphamide, cyclosporine, and hIVIG (see Chapter 103). None of these drugs has been extensively evaluated in dogs with ITP, but they may be useful in treatment of refractory cases. Splenectomy may also be indicated in dogs with ITP that have chronic relapses after tapering prednisone and azathioprine therapy (see Chapter 103).

**Supportive care.** Supportive care for dogs with ITP is critical to a positive outcome. Cage rest and exercise restriction to prevent trauma, eliminating all except absolutely necessary diagnostic procedures, and minimizing other invasive procedures will decrease risk of hemorrhage. A balance between appropriate monitoring and minimizing venipuncture is important. Careful monitoring for clinically significant changes that could be from new hemorrhage, especially involving the nervous system or eye, should be performed frequently. Blood transfusions should be administered to actively bleeding patients and those with clinically significant anemia. The only blood products that provide clinically significant platelet activity are fresh whole blood, platelet-rich plasma, and platelet concentrate. Fresh whole blood often provides enough platelets to stop an episode of clinical bleeding, although an increase in the platelet count is not expected. The beneficial effect of a fresh whole blood transfusion typically lasts approximately 48 hours. Blood typing of the donor and cross-matching of the recipient should be performed as described in Chapter 83. Platelet-rich plasma or platelet concentrate are the ideal products for administration to actively bleeding patients before they become anemic. However, availability and cost limit their use in most hospitals. Administration of gastric protectants such as H<sub>2</sub> blockers (e.g., famotidine), or proton pump inhibitors (e.g., omeprazole) and sucralfate may help prevent adverse effects of glucocorticoid treatment on the gastrointestinal tract, especially in dogs with gastrointestinal bleeding.

Treatment of Evans syndrome (concurrent IMHA and ITP) is managed as described for IMHA. However, azathioprine should be administered in addition to glucocorticoids. One dose of vincristine should be considered if the thrombocytopenia is severe (platelet count less than 15,000/µL). Whole blood transfusion rather than pRBCs should be administered in dogs with Evans syndrome that are actively bleeding. Dogs with Evans syndrome should not be treated with heparin because of the risk of hemorrhage.

# **Prognosis**

The prognosis for dogs with ITP is good to guarded, with a mortality rate of approximately 30%. Most dogs respond to medical treatment, although relapse is common, occurring in as many as 50% of dogs. Dogs with megakaryocytic hypoplasia have a more guarded prognosis. The prognosis for dogs with concurrent IMHA and ITP is poor, with a reported mortality rate of 80% or higher. See Chapter 87 for more information on this topic.

# IMMUNE-MEDIATED NEUTROPENIA

# **Etiology**

Autoimmune causes of neutropenia are rare in dogs and cats, accounting for approximately 0.4% of cases of neutropenia (see Chapter 85). In immune-mediated neutropenia (also called *idiopathic neutropenia* or *steroid-responsive neutropenia*), serum antineutrophil IgG antibodies can be detected by flow cytometry in the serum (Weiss, 2007). Antibody and complement directed against myeloid cells within the bone marrow have also been identified. In most cases of suspected immune-mediated neutropenia, the diagnosis is one of

exclusion because commercial testing for antineutrophil antibodies is not readily available. As with other immune-mediated disorders, immune-mediated neutropenia may be a primary disorder or occur secondary to drug therapy, neoplasia, or other immune-mediated disorder (Table 104-7). The majority of canine cases reported in the literature have been primary. Only one case of suspected immune-mediated neutropenia in a cat has been reported.

### **Clinical Features**

In a retrospective report of 11 dogs with suspected immunemediated neutropenia, a variety of breeds were represented and eight of 11 cases were female (Brown et al., 2006). Affected dogs were typically young, with a median age of 4 years. Clinical signs included fever, lameness, anorexia, and lethargy and the duration of clinical signs ranged from 3 to 180 days. Common abnormalities detected on CBC, serum biochemistry panel, and urinalysis included severe neutropenia (median 110 cells/µL), mild anemia, hyperglobulinemia, and increased alkaline phosphatase level. Further evaluation of affected dogs with bacterial culture, infectious disease serology, and imaging did not reveal a cause for the neutropenia. Bone marrow cytology and histopathology revealed myeloid hyperplasia in the majority of affected dogs and myeloid hypoplasia in two dogs. All dogs had resolution of neutropenia 1 to 18 days after initiation of treatment with glucocorticoids.

## **Diagnosis and Treatment**

A clinical diagnosis of immune-mediated neutropenia is made by exclusion of other causes of neutropenia and by rapid response to treatment with glucocorticoids at an initial dose of 2 to 4 mg/kg/day of prednisone. Gradual withdrawal of corticosteroid therapy is possible without relapse in most dogs; however, some dogs require long-term immunosuppression. Routine monitoring is important to detect recurrence of neutropenia and monitor for infection. See Chapter 85 for more information on this topic.

### IDIOPATHIC APLASTIC ANEMIA

Aplastic anemia (aplastic pancytopenia) is characterized by cytopenia of all three marrow-derived cell lines and a hypo-



Causes of Severe Neutropenia in Dogs and Cats

ETIOLOGY	EXAMPLE
Infection	Parvovirus, ehrlichiosis, bacterial sepsis
Drug associated	Chemotherapeutic agents, cytotoxic drugs, vincristine, estrogens, trimethoprim/ sulfadiazine, phenobarbital
Bone marrow suppression	Aplastic anemia, Ehrlichia canis infection, myelodysplasia, myeloid hypoplasia, leukemia
Immune mediated	Primary immune-mediated neutropenia

cellular/acellular bone marrow, with the marrow elements replaced by adipose tissue. Reported causes of aplastic anemia in dogs and cats include infectious agents (Ehrlichia spp, parvovirus, sepsis, feline leukemia virus, feline immunodeficiency virus) hormonal (estrogens), drug associated, radiation associated, and idiopathic. By definition the cause of idiopathic aplastic anemia is unknown; however, evidence in humans suggests that it may be immune mediated. Although an immune-mediated cause has not been established for idiopathic aplastic anemia in dogs and cats, trial therapy with prednisone, cyclosporine, or both may be considered once other causes of aplastic anemia, most notably infectious agents, have been ruled out. An immune-mediated cause for idiopathic anemia is currently difficult to prove but should be suspected in cases that respond to immunosuppressive therapy. The prognosis for idiopathic aplastic anemia is generally guarded to poor. See Chapter 86 for more information on this topic.

### **POLYARTHRITIS**

# Etiology

Immune-mediated polyarthritis is defined as chronic synovial inflammation in two or more joints, failure to isolate an organism from the joint fluid, and a positive response to immunosuppressive therapy. Immune-mediated polyarthritis is primarily a type III immune complex hypersensitivity disorder (see Chapter 101) in which immune complexes are deposited in the synovial membrane, initiating local

inflammation and release of proteolytic enzymes and cytokines, with resultant cartilage degeneration. In rheumatoid arthritis type IV hypersensitivity may also be present with perivascular infiltration of mononuclear cells into the synovial membrane (see Chapter 101). Immune-mediated polyarthritis may be classified as primary or secondary. In secondary polyarthritis immune complex deposition in the joints is secondary to an underlying inflammatory or neoplastic disease. Infectious agents are an important cause of secondary polyarthritis. Chronic bacterial infections may cause secondary or reactive polyarthritis, and Anaplasma spp., Ehrlichia spp., and Borrelia burgdorferi also cause polyarthritis, although they cannot usually be visualized in or cultured from affected joints. Administration of live calicivirus vaccine also causes transient polyarthritis in cats.

In primary immune-mediated polyarthritis no underlying cause of polyarthritis can be identified. This form of polyarthritis is believed to be attributable to an underlying immune system dysfunction or imbalance (true autoimmunity; see Chapter 101). The most commonly recognized forms of polyarthritis in the dog and cat are idiopathic nonerosive polyarthritis, reactive nonerosive polyarthritis secondary to underlying inflammatory disease (gastrointestinal disease, chronic inflammation, neoplasia, or infection), rheumatoid arthritis, and proliferative polyarthritis (Table 104-8). A number of breed-specific syndromes are recognized in dogs. A nonerosive polyarthritis is also a prominent feature of SLE. See Chapter 74 for a more detailed discussion of the various forms of polyarthritis.



TABLE 104-8

Forms of Polyarthritis Recognized in Dogs and Cats

SYNDROME	CLINICAL MANIFESTATIONS	BREED PREDISPOSITION
Idiopathic nonerosive	Small distal joints	Large-breed dogs, rarely cats
Secondary nonerosive	Similar to idiopathic but clinical signs of underlying disease also present	Any breed
Breed-specific idiopathic nonerosive	Similar to idiopathic but more severe and often concurrent meningeal inflammation	Akita, Weimaraner, Newfoundlands
Familial Sharpei fever	Recurrent fever, soft tissue swelling around affected joints, predisposition to systemic amyloidosis	Sharpei
Lymphoplasmacytic synovitis	No sign of systemic illness, cranial cruciate rupture, lymphocytes and plasma cells in synovial fluid	Rottweiler, Labrador Retrievers, Newfoundlands, Staffordshire Terriers
SLE	Multisystemic immune disease	German Shepherd dogs, rarely cats
Rheumatoid arthritis	Initially similar to nonerosive form but progresses to joint crepitus, laxity, luxation, and deformity of affected joints (carpi, hocks, phalanges)	Small and toy breeds
Erosive polyarthritis of greyhounds	Erosive changes in phalanges, carpi, hocks, elbow, stifles; lymphoplasmacytic inflammation in synovial fluid	Young Greyhounds
Feline chronic progressive polyarthritis	Erosive or proliferative changes in multiple joints	Young male cats infected with FeFSV or feline leukemia virus



# BOX 104-5

# Clinical Signs of Polyarthritis in Dogs and Cats

#### Dogs

- Palpable joint swelling
- Distension of joint capsule
- Shifting leg lameness
- Unwillingness to rise
- · Hesitant or "walking on eggshells" gait
- Joint pain
- Fever
- Anorexia
- Lethargy
- Cervical pain

#### Cats

- Palpable joint swelling
- Distension of joint capsule
- Joint pain
- Fever
- Anorexia
- Lethargy
- Generalized hyperesthesia
- Decreased activity/hiding

#### **Clinical Features**

The clinical hallmark of immune-mediated polyarthritis is the presence of nonseptic inflammation within the synovial membrane of two or more joints. Consequently the diagnosis is made by analysis of synovial fluid collected from joints suspected to be affected. Common clinical signs are listed in Box 104-5. In some cases neurologic disease is initially suspected because the animal is unable to ambulate; however, the neurologic examination in dogs with polyarthritis is normal. Many dogs and cats with polyarthritis have clinical signs of systemic illness, including fever, anorexia, and lethargy. In some cases joint pain and swelling may be mild or not clinically detected and fever is the only clinical sign. Polyarthritis is one of the most common causes of unexplained fever in dogs. Joint pain from polyarthritis may also cause cervical pain, and concurrent meningeal inflammation has been reported in dogs with polyarthritis (Webb et al., 2002). Polyarthritis should therefore be considered in any dog or cat presenting with cervical pain without neurologic deficits. Cats with polyarthritis may appear to have generalized hyperesthesia and resist handling. Cats may also present for decreased activity, and the owners often note that the animal has become withdrawn, often hiding in inaccessible locations. In the less-common erosive forms of polyarthritis, affected joints may become distorted or collapsed as the disease progresses, resulting in a severe gait abnormality. These changes are typically irreversible.

# **Diagnosis**

Diagnosis of immune-mediated polyarthritis is made by documentation of inflammation within the synovial fluid,

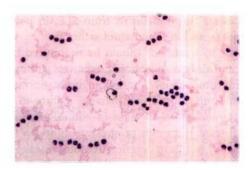


FIG 104-6
Direct smear of synovial fluid from a dog with idiopathic immune-mediated polyarthritis. Note the presence of increased numbers of nondegenerate neutrophils.

synovial membrane, or both (Fig. 104-6). Synovial fluid for cytologic evaluation and culture should be collected from at least three and preferably four joints. Synovial fluid should be collected from the more distal joints (carpus, tarsus, stifle) because these are the most commonly affected. The approach to joint fluid collection is discussed in Chapter 73. Joint fluid may be grossly turbid, with decreased viscosity and increased volume. Cytologic evaluation reveals neutrophilic inflammation with no evidence of sepsis. Fluid should always be collected for culture and sensitivity to rule out an occult infection (especially likely if the animal has been previously treated with antibiotics). Once inflammation within multiple joints has been documented, the next step is to identify the type of polyarthritis (see Table 104-8) and whether it is from a primary autoimmune disease or secondary to underlying inflammation, infection, or neoplasia. Diagnostic tests should include a CBC, biochemistry profile, urinalysis, urine culture, thoracic radiographs, abdominal ultrasound, and infectious disease titers or SNAP test (E. canis, A. phagocytophilum, B. burgdorferi) (SNAP test, IDEXX, Westbrook, Maine). In some cases blood cultures may also be indicated. In dogs with suspected rheumatoid arthritis, a rheumatoid factor test should be performed (see Chapter 102). In dogs and cats with evidence of multiple organ involvement, an antinuclear antibody (ANA) titer is indicated to investigate for SLE (see Chapter 102).

#### **Treatment**

Treatment of secondary immune-mediated polyarthritis depends on identification of an underlying cause. Polyarthritis usually resolves with appropriate treatment and use of antiinflammatory doses of glucocorticoids or nonsteroidal antiinflammatory drugs. In dogs with primary (autoimmune) polyarthritis, immunosuppressive dosages of glucocorticoids are the initial treatment of choice (2 to 4 mg/kg/day). Additional immunosuppressive treatment is necessary in dogs that do not respond to corticosteroids alone or that relapse as glucocorticoids are withdrawn. Drugs that are useful include azathioprine, cyclophosphamide, and cyclosporine. Azathioprine is typically the first drug added to the treatment regimen. More aggressive immunosuppression is

often necessary in polyarthritis from SLE, in polyarthritis seen in Akitas, and in rheumatoid arthritis.

Response to treatment should be monitored by assessment of clinical signs and cytologic changes within the joint fluid. Joint fluid should be cytologically normal before tapering immunosuppressive therapy. Failure to establish cytologic remission in addition to clinical remission may result in disease relapse or progressive injury to the joints that ultimately results in degenerative joint disease. Approximately 80% of dogs with idiopathic nonerosive polyarthritis treated with prednisone alone respond well to initial treatment, and half of these dogs can be weaned off therapy after 3 to 4 months. The prognosis for idiopathic nonerosive polyarthritis is good, with a mortality/euthanasia rate of less than 20%. Relapses are common, however, and some dogs require life-long therapy. The prognosis for other forms of immune-mediated polyarthritis varies with the different forms of the disease. See Chapters 73 and 74 for more information on this topic.

## SYSTEMIC LUPUS ERYTHEMATOSUS

# **Etiology**

SLE is a multisystemic immune disorder in which antibodies to specific tissue proteins (type II hypersensitivity) and immune complex deposition (type III hypersensitivity) result in immune-mediated damage to multiple organs. Type IV mechanisms (delayed hypersensitivity) may also contribute to tissue damage. The underlying cause of SLE is still poorly understood, but an increased CD4/CD8 ratio, increased expression of a T-cell activation marker, and marked lymphopenia have been reported in dogs with active disease. These findings suggest that T-suppressor cells may be defective in dogs with SLE. The disease is heritable although not by simple autosomal mechanisms. Breeds that are predisposed include the German Shepherd dog, Shetland Sheepdog, Collie, Beagle, and Poodle. Several colonies of dogs with a high predisposition toward SLE have been established, and an association with certain MHC (DLA) types exists. Other risk factors likely include environmental factors and exposure to certain infectious agents and drugs.

# **Clinical Features**

The disease is uncommon in dogs and rare in cats. In dogs SLE most commonly occurs in middle-aged dogs (age range, I to 11 years), and there is no sex predisposition. Because any organ system may be affected in SLE, a wide range of clinical signs is possible. The most common signs are fever (100%), lameness or joint swelling from nonerosive polyarthritis (91%), dermatologic manifestations (60%), and signs of renal failure such as weight loss, vomiting, polyuria, and polydipsia. Proteinuria from glomerulonephritis is detected in 65% of patients. The dermatologic lesions often involve areas of skin exposed to sunlight, with photosensitization being common. The dermatologic manifestations are highly variable, with alopecia, erythema, ulceration, crusting, or

hyperkeratosis common. Mucocutaneous lesions may also occur. Other clinical manifestations may include hemolytic anemia, PRCA, thrombocytopenia, leukopenia, myositis, pleuropericarditis, and central nervous system dysfunction. A similar spectrum of disease manifestations has been reported in cats with SLE. SLE typically has a relapsing and remitting course, and different organ systems may be involved with subsequent relapses. For example, a dog initially presenting with clinical signs predominantly relating to the neuromuscular system (polyarthritis or myositis) may later relapse with signs of IMHA or ITP.

# Diagnosis

A diagnosis of SLE should be suspected when evidence of involvement of more than one organ system is present in a dog or cat with immune-mediated disease. Because of the large number of organ systems that may be involved, the diagnostic testing required varies widely from patient to patient. Diagnostic tests that should be performed in all dogs and cats with suspected SLE include a CBC, serum biochemical profile, urinalysis, quantitation of urine protein, collection of synovial fluid for cytology and culture, and fundic examination. Additional tests that may be indicated include thoracic and abdominal radiographs (investigating fever), abdominal ultrasonography (investigating renal dysfunction), infectious disease titers (investigating fever, thrombocytopenia, hemolytic or nonregenerative anemia, proteinuria, or polyarthritis), Coombs test (in presence of hemolytic anemia), bone marrow aspirate and core (in cases of cytopenia), and skin or kidney biopsy if dermatologic or renal lesions are present. The extent of diagnostic testing for infectious disease will depend on the species and geographic location. For example, testing for feline leukemia virus, feline immunodeficiency virus, and feline infectious peritonitis should be considered in any cat with suspected SLE. In dogs in Europe, testing for leishmaniasis should be strongly considered because this disease can mimic SLE.

Numerous criteria for the diagnosis of SLE in dogs have been extrapolated from the literature in humans. The most commonly accepted and clinically applicable criteria are shown in Table 104-9. Measurement of serum ANA titers is a relatively sensitive test to confirm the diagnosis of SLE, although the sensitivity reported in the literature ranges from 50% to 100% (see Chapter 102). The variability in diagnostic sensitivity probably arises from variation in the diagnostic criteria for confirming the diagnosis as well as variations in the populations of dogs tested. When used in dogs that have appropriate clinical criteria for SLE, the ANA test is an excellent test; however, false-positive results can occur in dogs and cats with other inflammatory or infectious disorders or neoplasia. ANAs are detected in 10% to 20% of dogs with seroreactivity to Bartonella vinsonii, Ehrlichia canis, and Leishmania infantum. Dogs with seroreactivity to multiple pathogens are more likely to be ANA positive. A recent study of 120 dogs in which an ANA titer was measured emphasized the importance of appropriate patient selection for testing (Smee et al., 2007). In this study measurement of an ANA titer was not a



Criteria for Diagnosis of SLE

MAJOR SIGNS	MINIMUM DIAGNOSTIC TESTING NECESSARY TO SUBSTANTIATE MAJOR SIGN	MINOR SIGNS	DIAGNOSTIC TEST NEEDED TO SUBSTANTIATE
Polyarthritis	Synovial fluid analysis and culture	Fever of unknown origin	Abdominal radiographs, urine culture, no response to antibiotics
Dermatologic lesions (consistent with SLE)	Skin scraping, skin biopsy	CNS signs	CT or MRI scan, CSF tap with infectious disease serology
ĠŇ ,	Urine protein/creatinine ratio >2, renal biopsy useful but not required	Oral ulceration	Biopsy of lesions
Polymyositis	Increased creatinine kinase or muscle biopsy demonstrating inflammation	Lymphadenopathy	Lymph node aspirate
Hemolytic anemia	Regenerative anemia, positive Coombs test, bone marrow aspirate if anemia not regenerative, negative infectious disease testing	Pericarditis	Echocardiography
Immune-mediated thrombocytopenia	Bone marrow aspirate, negative infectious disease testing	Pleuritis	Thoracic radiographs, thoracocentesis
Immune-mediated leukopenia	Bone marrow aspirate, negative infectious disease testing		

A diagnosis of SLE is considered confirmed if there are two major signs compatible with SLE and the antinuclear antibody (ANA) titer or LE test is positive or if there is one major sign and two minor signs and the ANA test or LE test is positive. A diagnosis is considered probable if there is only one major sign or two minor signs and a positive ANA titer (or LE test), or if there are two major signs and a negative ANA titer. Immune-mediated hemolytic anemia in conjunction with immune-mediated thrombocytopenia (Evans syndrome) is not considered to be a diagnosis of SLE unless there is an additional major or minor sign. Not all testing listed above is necessary in all cases. Specific diagnostic test will depend on the individual case presentation and geographic location.

Modified from Marks SL, Henry CJ: CVT update: diagnosis and treatment of systemic lupus erythematosus. In Bonagura JD: Kirk's current veterinary therapy XIII: small animal practice, ed 13, Philadelphia, 2000, WB Saunders, p 514.

SLE, Systemic lupus erythematosus; GN, glomerulonephritis, CNS, central nervous system; CT, computed tomography; MRI, magnetic

useful diagnostic test in dogs without any major clinical or clinicopathologic abnormalities suggestive of SLE. Only one of 47 dogs tested that did not have any major signs of SLE had immune-mediated disease, and this dog was seronegative for ANA. Ten (21%) of 47 dogs were seropositive for ANA. Conversely, 13 of 16 dogs with two major signs compatible with SLE had immune-mediated disease, and ANA was positive in 10 of these dogs. These results emphasize that the positive predictive value of a diagnostic test is lower in a population of animals in which the disease prevalence is low.

resonance imaging; CSF, cerebrospinal fluid; LE, lupus erythematosus.

The LE test is rarely used clinically for diagnosis of SLE because of very low sensitivity. A number of other antibody tests have been investigated in groups of dogs with SLE, including antinative DNA antibodies, antiextractable nuclear antigen antibodies, and antihistone antibodies. None of these tests has been extensively evaluated in dogs, and none is currently commercially available.

#### **Treatment**

Immunosuppressive therapy for SLE begins with high doses of corticosteroids (1 to 2 mg/kg q12h). The dose is then tapered if disease remission is achieved. Addition of other cytotoxic drugs (e.g., azathioprine, cyclophosphamide,

cyclosporine) is usually necessary to induce or maintain remission. Little information is available on the efficacy of drug protocols for treating SLE. One study reported a protocol of prednisone (0.5 to 1.0 mg/kg q12h) combined with levamisole (2 to 5 mg/kg [maximum 150 mg per patient] every other day; Chabanne et al., 1999b). The prednisone is tapered over a 1- to 2-month period and the levamisole continued for 4 months. In cases that relapse, levamisole is administered for a further 4 months. This protocol was effective in inducing remission in 25 of 33 dogs with SLE. The prognosis for dogs with SLE is guarded to poor. Relapse is common regardless of the drug protocol used, and longterm and often life-long immunosuppressive therapy is necessary to control the disease. Relapses may involve different organ systems and clinical signs than at initial presentation (e.g., hemolytic anemia initially and polyarthritis at relapse).

### **GLOMERULONEPHRITIS**

### Etiology

Acquired glomerulonephritis (GN) is more common in dogs than cats and results from the presence of immune complexes within the glomerular capillary walls. Immune complexes may be circulating antigen-antibody complexes that are deposited or trapped in the glomerulus or may form in situ when circulating antibodies react with either endogenous glomerular antigens or nonglomerular antigens within the glomerular capillary wall. Soluble circulating immune complexes formed in the presence of mild antigen excess, or when both antigen and antibody are present in approximately equal quantities, may be deposited along capillary walls resulting in a granular pattern observed on immunofluorescent or immunoperoxidase staining. Infectious and inflammatory diseases are common identifiable causes for deposition of immune complexes within the glomerulus (Box 104-6). Unfortunately in the majority of cases of GN, an underlying cause is not identified. When immune complexes form in situ, a smooth linear pattern is observed with immunofluorescent or immunoperoxidase staining. Causes of in situ deposition of immune complexes may be either true autoimmune disease when antibodies are directed against the basement membrane of the glomerular capillaries (not yet documented as a spontaneous disease in dogs and cats) or when antigen becomes localized in the glomerular capillary wall. For example, in dogs with heartworm disease, soluble Dirofilaria immitis antigens have been shown to adhere to the glomerular capillary wall by a carbohydrateglycoprotein interaction.

Whatever the cause of immune complex deposition, the consequences are similar (see Chapter 43) and ultimately lead to severe proteinuria, systemic hypertension, renal failure, and predisposition to thromboembolism.

### **Clinical Features**

The hallmark of GN is proteinuria, which is readily detected on routine urinalysis. In many cases proteinuria is initially identified as an incidental finding and the animal may have no obvious clinical signs or only subtle abnormalities (e.g., weight loss, lethargy, decreased appetite). In other cases animals present with clinical signs of renal failure (e.g., anorexia, weight loss, vomiting, polyuria, polydipsia), and proteinuria is identified in the course of the evaluation. In nephrotic syndrome, which is defined as the presence of proteinuria, hypoalbuminemia, hypercholesterolemia, and



BOX 104-6

Infectious and Inflammatory Diseases Implicated in Pathogenesis of GN in Dogs

- Ehrlichiosis
- Dirofilariasis
- Leptospirosis
- Borreliosis
- Brucellosis
- Endocarditis
- Pyelonephritis
- Prostatitis

GN, Glomerulonephritis.

either edema or ascites, the clinical signs are more severe and often rapidly progressive. Other clinical signs in dogs with glomerulonephritis may relate to the presence of hypertension or hypercoagulability. Hypertension may result in retinal changes and blindness, whereas TEs may occur as a result of the hypercoagulable state.

# **Diagnosis**

A diagnosis of protein-losing nephropathy is made by documentation of persistent proteinuria that cannot be explained by inflammation of the lower urinary tract or blood contamination of the urine. Initial dipstick estimates of urine protein should be evaluated in the light of the urine sediment and specific gravity of the urine. The severity of protein loss should then be quantitated by measurement of a protein/ creatinine ratio, preferably on a urine sample with no inflammation or hematuria. A protein/creatinine ratio greater than 0.5 is abnormal; most dogs and cats with protein-losing nephropathy have a ratio greater that 2.0. Once persistent proteinuria has been documented, further testing is necessary to determine whether evidence of tubular dysfunction also exists and to investigate for the presence of underlying infectious or inflammatory diseases implicated as causes of GN. Diagnostic tests that should be performed include a CBC, serum biochemical profile, urinalysis and urine culture, blood pressure, and radiographs of the thorax and abdomen. Ultrasonography of the kidneys is useful to investigate for evidence of pyelonephritis, nephroliths, or other underlying renal disease, but it rarely detects changes associated with glomerulonephritis. An occult heartworm test should be performed and serum titers submitted for the infectious diseases discussed in Box 104-6. Testing for hyperadrenocorticism should be considered in dogs if the appropriate signalment and clinical signs are present. Renal biopsy should be considered if an underlying cause for the proteinuria cannot be identified. Tissue samples should be submitted for routine histopathology, electron microscopy, and immunopathology. Goals of renal biopsy should be to confirm the underlying disease process (specific type of GN, hereditary nephritis, glomerulosclerosis, amyloidosis), determine severity of the disease and, if possible, determine a prognosis as well as guide specific therapy.

#### **Treatment**

Therapy for immune-mediated glomerulonephritis should be directed at treating the underlying disease (if identified), decreasing protein loss in the urine, decreasing the likelihood of thromboembolism, and initiating appropriate dietary therapy and supportive care. Angiotensin converting enzyme inhibitors (ACEI) (e.g., enalapril 0.25-0.5 mg/kg q12-24h) are currently the most effective treatment for proteinuria. Anticoagulation is recommended to decrease the likelihood of thromboembolism in dogs with GN, especially in those with documented antithrombin deficiency (less than 70%). Low-dose aspirin (0.5 mg/kg q24h) may be beneficial for its anticoagulant effects and for decreasing the glomerular response to immune complexes. Other supportive measures include control of hypertension (if not controlled by ACEI

alone); dietary sodium restriction; a low-protein, highquality protein diet with n-3 fatty acid supplementation; and control of ascites and edema if present. Therapy for overt renal failure may also be necessary. See Chapter 44 for further details on general management of renal failure.

In theory, immunosuppression should be useful in idiopathic immune-mediated GN; however, no studies have documented beneficial responses to immunosuppressive therapy in dogs with GN, and the use of corticosteroids may exacerbate rather than ameliorate proteinuria. Immunosuppressive therapy is indicated when glomerulonephritis occurs as part of an immune-mediated disease known to respond to corticosteroids, such as SLE. Other indications for immunosuppressive treatment are currently poorly defined.

Careful monitoring of response to therapy with monthly measurement of protein/creatine ratios, blood urea nitrogen, creatine, and blood pressure is important to assess adequacy of therapy. Prognosis for GN varies depending on the severity of disease, underlying histopathology, and response to treatment. In general, the prognosis is guarded in animals that initially present with concurrent azotemia. The outcome is best in dogs with reversible causes of immune complex deposition and those that respond to diet and ACEI to control proteinuria. See Chapter 43 for more information on this topic.

# **ACQUIRED MYASTHENIA GRAVIS**

Myasthenia gravis (MG) is a disorder of neuromuscular transmission resulting from deficiency or dysfunction of the nicotinic acetylcholine receptor (AChR) on the postsynaptic membrane. Acquired myasthenia gravis is an autoimmune disease in which antibodies directed against the AChR interfere with the interaction between acetylcholine and its receptor. Antibodies also cross-link AChR and cause receptor internalization. Complement-mediated damage to the postsynaptic membrane also contributes to neuromuscular blockade. As with other immune-mediated diseases, MG may be a primary autoimmune disorder or occur in association with other disorders, such as thymoma, and other neoplasms. Hypothyroidism and hypoadrenocorticism, which are also immune-mediated disorders, may also occur in association with MG. A breed predisposition exists for MG in dogs, with the Akita, various terrier breeds, and German Short-Haired Pointer being at increased risk. Abyssinian and Somali cats also have an increased risk of MG compared with other breeds.

The most common clinical presentation of MG is generalized weakness (60% of cases), either with or without concurrent megaesophagus. In focal MG, in which signs of generalized weakness are absent, the most common clinical sign is regurgitation because of megaesophagus, but dysphagia, voice change, and cranial nerve dysfunction may also occur. An acute fulminating form of MG is characterized by severe weakness, sometimes with loss of spinal reflexes and usually in conjunction with megaesophagus and aspiration pneumonia. In cats, the two most common clinical presentations are generalized weakness without megaesophagus and generalized weakness associated with a cranial mediastinal mass.

Definitive diagnosis of MG is by measurement of serum autoantibodies against AChR by immunoprecipitation radioimmunoassay. The assay is sensitive and specific and false-positive results are rare. Seronegative MG occurs in only 2% of dogs with MG. Canine and feline specific assay systems should be used. Immunosuppressive doses of corticosteroids lower the antibody concentration and can interfere with testing. Because antibodies are not the cause of congenital MG, results of antibody testing will be negative. Other useful tests in diagnosis of MG include evaluation of the response of clinical signs to a short-acting anticholinesterase drug (edrophonium chloride [Tensilon]) and electrodiagnostic testing. Once a diagnosis of MG has been confirmed, additional testing is necessary to investigate for the presence of other underlying disorders that may lead to secondary MG or occur concurrently.

The first line of treatment for MG is oral or injectable anticholinesterase inhibitors such as neostigmine or pyridostigmine (Table 104-10). These drugs act by prolonging the action of acetylcholine at the neuromuscular junction. Immunosuppression with glucocorticoids should be considered in patients that do not respond well to anticholinesterase inhibitors alone. The advantages of the immunosuppressive effects of glucocorticoids in MG are often outweighed by adverse effects such as worsening of muscle weakness and muscle atrophy. Corticosteroids may be problematic in animals with aspiration pneumonia, diabetes mellitus, and gastrointestinal ulceration, and if corticosteroids are necessary for MG care should be used to avoid excessive doses. Therapeutic approaches include starting glucocorticoids at the low end of the immunosuppressive range (prednisone 1 mg/kg q12h) or starting glucocorticoids at an even lower dose (prednisone 0.5 mg/kg PO every other day) and slowly increasing the dose after 2 weeks if a satisfactory response is not seen. Other immunosuppressive drugs that have been used for adjunctive management of MG include azathioprine and cyclosporine. Drug regimens and doses used in the routine management of MG are given in Table 104-10.

Spontaneous remission of acquired MG is common in dogs. Clinical remission is accompanied by a decrease of the AChR antibody titer into the reference range. Repeated measurement of the AChR titer is a useful guide for identifying when clinical remission is occurring and when adjustments to therapy may be indicated. The majority of dogs that do not go into remission have underlying neoplasia. See Chapter 71 for more information on this topic.

# **IMMUNE-MEDIATED MYOSITIS**

### **MASTICATORY MYOSITIS**

Masticatory myositis is a focal myositis affecting the muscles of mastication (temporalis, masseter, digastricus). Masticatory muscles contain a unique muscle fiber type (type 2M) that differs histopathologically, immunologically, and bio-



Drug Regimens and Doses Used for Routine Management of MG in Dogs and Cats

DRUG	DOGS	CATS
Pyridostigmine	0.5-3.0 mg/kg PO q8-12h	0.25-3.0 mg/kg PO q8-12h (start at low end of dose)
Neostigmine (use to bypass gastrointestinal tract in presence of severe regurgitation)	0.04 mg/kg IM qóh	0.04 mg/kg IM q6h
Prednisone	0.5 mg/kg PO q48h to 1.0 mg/kg q12h	0.5 mg/kg PO q48h to 1.0 mg/kg q12h
Azathioprine	2 mg/kg PO q24h	Do not use in cats
Cyclosporine	5 mg/kg PO q24h to 10 mg/kg PO q12h (see Chapter 103)	0.5-3 mg/kg PO q12h (microemulsified)

MG, Myasthenia gravis.

chemically from fiber types in limb musculature. Antibodies directed against this unique muscle fiber type are present in more than 80% of dogs with masticatory myositis.

Masticatory myositis is the most common form of myositis that occurs in dogs. It has not been reported in cats. Young large-breed dogs are overrepresented, and there is no breed or gender predisposition. Clinical signs include inability to open the mouth (trismus), swelling and/or pain of the masticatory muscles, and severe muscle atrophy. In some dogs an acute phase is recognized in which muscle swelling and pain predominate. If untreated this acute phase progresses to a chronic phase characterized by severe muscle atrophy and trismus. In many affected dogs the acute phase is not recognized and the first clinical signs that are recognized are severe muscle atrophy and inability to open the jaws. In severe cases the jaws can only be separated by a few centimeters, and the affected animal is unable to eat or drink. Less severely affected dogs may be able to use the tongue to lick up fluids or liquidized food. Other clinical signs include fever, depression, weight loss, dysphagia, dysphonia, and exophthalmus from swelling of the pterygoid muscles.

Diagnosis of masticatory myositis is made based on the characteristic clinical signs, and presence of antibodies against type 2M fibers. This test is positive in greater than 80% of cases and has a specificity approaching 100%. Muscle biopsy is useful to determine the degree of fibrosis and likelihood of return to normal function with treatment and to confirm the diagnosis in dogs in which the antibody test is negative. Multifocal infiltration with lymphocytes, histiocytes, and macrophages, with or without cosinophils, is found on histopathology. Moderate to severe muscle fiber atrophy, fibrosis, and sometimes complete loss of muscle fibers with replacement by connective tissue may be present. Other adjunctive tests that may be useful include measurement of creatinine kinase, which is increased in some but not all dogs with masticatory myositis, and electrodiagnostic testing, which allows identification of the most severely affected muscles. Typical electrodiagnostic findings include presence of fibrillation potentials and positive sharp waves.

Treatment of masticatory myositis relies on the use of immunosuppressive doses of corticosteroids (prednisone 2-4 mg/kg PO q24h). Under no circumstances should force be used to open the jaws because fracture or luxation of the temporomandibular joint may result. Once resolution of clinical signs is achieved with corticosteroids, the dose should then be slowly tapered over several months. Disease activity and progression should be monitored by clinical signs (especially range of motion) and measurement of creatinine kinase (if elevated at presentation). Long-term treatment with prednisone or an additional immunosuppressive drug such as azathioprine is required in dogs that relapse when prednisone is tapered. Tapering of prednisone too quickly increases the chance of relapse. The goal of therapy is a return to normal muscle function and a normal quality of life. In many cases, especially in the presence of severe fibrotic changes, muscle atrophy persists and is exacerbated by glucocorticoid therapy. Prognosis for return to function is good in most cases. See Chapter 72 for more information on this topic.

#### **POLYMYOSITIS**

Polymyositis is characterized by multifocal or diffuse infiltration of skeletal muscle by lymphocytic cells with negative serology for infectious disease. Although most cases are primary autoimmune, paraneoplastic immune-mediated myositis may be associated with malignancies such as lymphoma (particularly in Boxers), bronchogenic carcinoma, myeloid leukemia, and tonsillar carcinomas in dogs. The specific inciting antigen is not known, although the mechanism of injury is believed to be mediated by cytotoxic T cells (type IV delayed-type hypersensitivity).

Polymyositis is uncommon in dogs and rare in cats. The disease is most common in young large-breed dogs, and Boxers and Newfoundlands are overrepresented. Clinical signs include generalized weakness that worsens with exercise and a characteristic stiff gait. Cervical ventriflexion may occur, especially in cats. Most animals show pain on palpation of affected muscles, particularly the proximal muscle groups. Dysphagia, generalized muscle atrophy, dysphonia, and fever may also be present. Megaesophagus has been



#### Infectious Causes of Polymyositis in Dogs

- Toxoplasma gondii
- Neospora caninum
- Borrelia burgdorferi
- Ehrlichia canis
- Rickettsia rickettsii
- Hepatozoon americanum

reported in 15% of cases. Some dogs with polymyositis also have signs of masticatory myositis, and these dogs are positive for antibodies against type 2M fibers. Polymyositis may also occur in SLE and in canine polyarthritis/myositis syndrome.

Diagnosis of polymyositis is based on characteristic clinical signs, presence of an elevated creatinine kinase level (more commonly increased in polymyositis than in masticatory myositis), electrophysiologic testing abnormalities consistent with myositis, and muscle biopsy. Muscle biopsy is very important in dogs with polymyositis to rule out infectious causes of myositis (Box 104-7). Muscle biopsies have similar changes to those described for dogs with masticatory myositis; however, the presence of eosinophils in dogs with polymyositis increases the index of suspicion for an infectious cause. Polymyositis may be a preneoplastic syndrome, especially in Boxers, so a complete evaluation for neoplasia should be performed in Boxers with polymyositis.

Treatment of polymyositis is similar to treatment of masticatory myositis (see previous page). Prognosis for return to function is good in most cases. See Chapter 72 for more information on this topic.

### **DERMATOMYOSITIS**

Dermatomyositis is an uncommon immune-mediated disorder affecting the skin, skeletal muscle, and vasculature of Collies and Shetland Sheepdogs. The disorder has an autosomal-dominant pattern of inheritance, and the pathogenesis is suspected to be immune complex deposition, although the target antigen is not known.

In dermatomyositis cutaneous lesions develop between 2 and 4 months of age, with signs of myositis developing later. The temporalis muscle is most commonly affected and clinical signs include dysphagia and muscle atrophy. More severe signs may include megaesophagus and generalized polymyositis with diffuse muscle atrophy, especially of the distal appendicular muscles. Diagnosis of dermatomyositis is based on the classic signalment (age, breed, presence of cutaneous signs). The creatinine kinase level is usually only minimally increased. Definitive diagnosis is based on skin and muscle biopsy.

Treatment of dermatomyositis relies on symptomatic care of cutaneous lesions and immunosuppression. The protocol for corticosteroid therapy is similar to that used for polymyositis, but prolonged therapy is needed and relapses are common. Additional recommendations include avoidance

of exposure to sunlight, neutering of sexually intact dogs, and vitamin E supplementation. Pentoxifylline has also been shown to be of some benefit in affected dogs (see Chapter 103). The prognosis depends on severity, being good for mild cases and poor for severely affected dogs. See Chapter 72 for more information on dermatomyositis.

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GENERIC NAME /TRADE		RECOMMENDED DOSE	
GENERIC NAME (TRADE NAME)	PURPOSE	DOG	CAT
Aspirin	Prevent thromboembolic complications of IMHA	0.5 mg/kg q24h	Not applicable
Azathioprine (Imuran) Chlorambucil (Leukeran)	Immunosuppression Immunosuppression	2 mg/kg q24h 0.1-0.2 mg/kg PO q24h initially, then taper to every other day once a response is seen	Not recommended 0.1-0.2 mg/kg PO q24h initially then q48h
Cyclophosphamide (Cytoxan)	Immunosuppression	50 mg/kg/day PO for 4 out of 7 days or 200 mg/kg IV once a week	2.5 mg/kg/day PO for 4 out of 7 days or 7 mg/ kg IV once a week
Cyclosporine (Atopica, Neoral, Sandimmune)	Immunosuppression	5 mg/kg q24h to 10 mg/kg q12h; start at lower end of dose for microemulsified products Lower doses of 1-2.5 mg/kg q12h if in conjunction with ketoconazole	0.5-3 mg/kg q12h (microemulsified products)
Danazol (Danocrine) Dexamethasone Enalapril (Enacard) Famotidine (Pepcid)	Immunosuppression Immunosuppression Treatment of proteinuria Treatment and prevention of gastric ulceration	5 mg/kg PO q12h 0.25-0.5 mg/kg PO q24h 0.25 to 0.5 mg/kg q12-24h 0.5-1.0 mg/kg PO/IM/SC q12-24h	5 mg/kg PO q12h 0.25-1.0 mg/kg PO q24h Not applicable 0.5 mg/kg PO/IM/SC q12-24h
Heparin (unfractionated) Hemoglobin-based oxygen carrier (Oxyglobin)	Anticoagulation Provision of oxygen- carrying support	200-300 U q6h 10-30 mL/kg as IV infusion	Not applicable Not recommended
hIVIG	Immunosuppression	0.25-1.5 g/kg as an IV infusion over 6-12 hours (one dose only)	Not applicable
Levamisole	Immunosuppression in SLE	2 to 5 mg/kg (maximum 150 mg per patient) every other day	Not applicable
Neostigmine (Prostigmin) Pentoxifylline Prednisone/prednisolone Pyridostigmine (Mestinon)	Anticholinesterase inhibitor Immunomodulation Immunosuppression Anticholinesterase inhibitor	0.04 mg/kg IM q6h 10-15 mg/kg PO q8h 2-4 mg/kg/day PO 0.5-3.0 mg/kg q8-12h	0.04 mg/kg IM q6h Not applicable 2-8 mg/kg/day PO 0.25-3.0 mg/kg q8-12h (start at low end of dose)
Sucralfate (Carafate)	To prevent drug-induced gastritis	0.5-1 g PO q6-12h	0.25-0.5 g PO q8-12h
Vincristine (Oncovin)	Increase platelet count in ITP	0.02 mg/kg IV as a single dose	Not applicable

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